Henry Ford Hospital Medical Bulletin

Vol. 3 No. 2

CONTENTS

	Page
1. Hypothermia and Artificial Hibernation ROBERT D. DRIPPS, M.D.	57
2. Evaluation of Methods of Treatment of Portal Hypertension WILLIAM A. ALTEMEIER, M.D.	62
3. Nutrition and Infection JOSEPH A. JOHNSTON, M.D.	68
4. Presenting the Diagnosis of Functional Illness EUGENE J. ALEXANDER, M.D.	71
5. Asthma in Children—Outcome in 100 Cases THADDEUS H. JOOS, M.D. AND ROBERT S. ELLIS, M.D.	73
6. Florence Nightingale and 100 Years of Modern Nursing FRANK R. MENAUGH, M.D.	76
7. The Artery Bank D. EMERICK SZILAGYI, M.D.	82
8. Psychotherapy C. B. FARRAR, M.D.	90
9. Psittacosis; Medical Symposium on Diagnosis and Treatment EDWARD L. QUINN, M.D. AND PANEL	97
10. Abstracts of Recent Publications of the Professional Staff of the Henry Ford Hospital and the Edsel B. Ford Institute for Medical Research	104

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HENRY FORD HOSPITAL MEDICAL BULLETIN

Published quarterly by the Professional Staff of the
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Vol. 3 June, 1955 No. 2

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Henry Ford Hospital
1955

HYPOTHERMIA AND ARTIFICIAL HIBERNATION

ROBERT D. DRIPPS, M.D.*

The basic aim ot hypothermia and/or "artificial hibernation" is to decrease tissue reactivity and metabolism, and hence permit viability under conditions of reduced supply of nutrients and reduced elimination of waste products. The concept is not new but at least two factors have caused a resurgence of interest in it. The first was the desire to operate upon the open heart — a circumstance under which this organ could not serve as a blood pump until closure was effected. Some means of decreasing the body's need for oxygen, glucose and other nutrients had to be devised, unless an artificial pump — oxygenator of the type proposed by Gibbon[1] or Dennis[2] could be used. The second factor was the synthesis of chlorpromazine by French chemists and the introduction by the French surgeon, Laborit[3], of drug-induced "artificial hibernation" in 1951. Certain physiological, pharmacological and chemical aspects of hypothermia and artificial hibernation will be presented in this paper,

True hibernation in such animals as the golden hamster, dormouse, hedgehog, woodchuck, ground squirrel or opossum differs in certain vital respects from the condition possible to induce in man either with cold or by drugs. The animals listed above can hibernate spontaneously when environmental conditions are proper, and, of even greater significance, can return themselves to normal, unaided. Man cannot do this. Shivering tends to minimize reduction in body temperature in the cold. Anesthesia or use of curarizing drugs are therefore necessary for a reasonably rapid reduction in temperature in man. Once this is achieved, man cannot warm himself, his survival depending upon careful attention to the support of respiration, circulation and reversal of the environmental temperature by attendants. The hibernating animal is self-sufficient; man is completely dependent upon others. Whether a hibernating gland is responsible for these differences remains to be determined.

Physiological Alterations with Cooling

1. *Metabolism*—oxygen consumption decreases progressively with cooling (Fig. 1). At 20° C (68°F) there is a 75 percent reduction in oxygen utilization.
2. *Circulation*—Pulse rate declines steadily as body temperature decreases. Figure 2 illustrates data obtained in the dog (after Ross)[4]. Bradycardia of a marked degree occurs with low temperature. In the hibernating hamster whose usual cardiac rate is 300-400 per minute a pulse rate of 4-6 per minute is common.

Blood pressure likewise falls continuously with body temperature. Figure 3 is compiled from experimental observations in the dog (Ross)[4]. Cardiac output is reduced by about 50 percent at 25° C (77° F). Plasma volume decreases slightly. There is a marked prolongation of the period of systole and isometric relaxation.

Myocardiac irritability increases, and death of the experimental animal or man from ventricular fibrillation is possible when body temperature is below 25° C. A characteristic series of changes occurs in the electrocardiogram as cooling continues. The P wave disappears, the QRS complex widens, is slurred, the S-T segment is evelated and the T wave inverts. Various degrees of heart block are noted; nodal rhythm may occur as well as ventricular extra-systoles.

*Professor of Anesthesiology, University of Pennsylvania Medical School

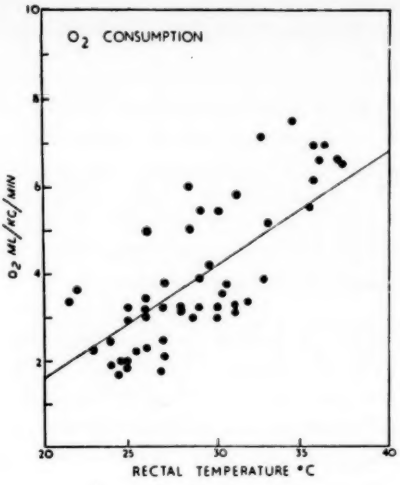


FIG. 1

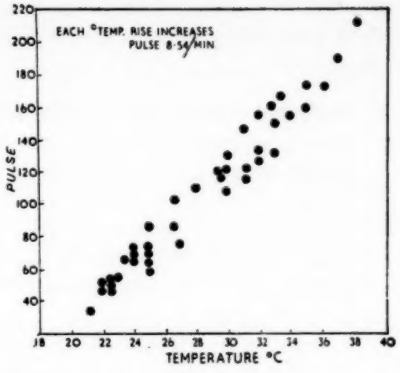


FIG. 2

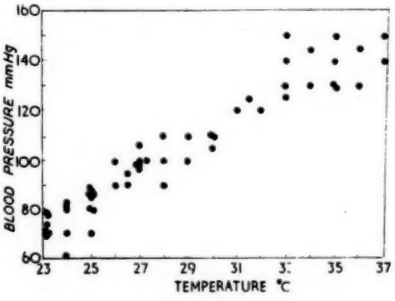


FIG. 3

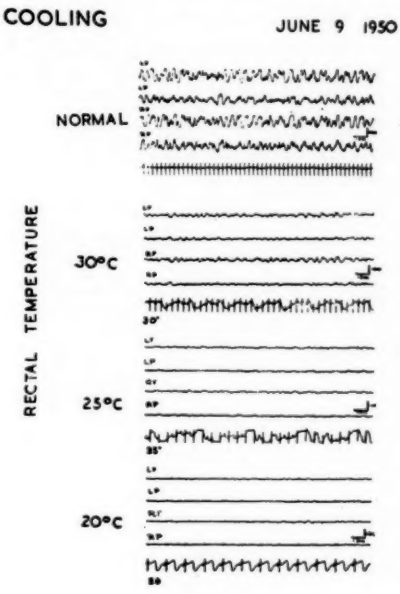


FIG. 4

The cause of these myocardial and conduction changes is not yet known, but certain aspects have been stressed. Anoxia has been implicated, as has hypercarbia (see respiration below). Potassium loss from the myocardium may occur. There appears to be an imbalance between sympathetic and parasympathetic influences on the heart, with a suggestion that vagal effects are reduced.

Reversal of ventricular fibrillation in the hypothermic state has proven difficult in many instances. Electrical defibrillation, so useful in treating this abnormality at normal body temperatures, has proven of less value during cooling according to some investigators. Swan and co-workers[5] have reported success with prostigmine. Others believe

that the heart must first be partially rewarmed before attempts at reversal are made. There seems little question that the heart is one of the weak links of hypothermic man and animals.

3. *Respiration*—Pulmonary ventilation is reduced as body temperatures falls. Spontaneous breathing will usually cease at 20° C. Respiration acidosis with a rise in arterial carbon dioxide tension and a decrease in blood pH developes. These changes can be prevented by artificial ventilation and should never be allowed to develop. Certain clinicians believe that hyperventilation and respiratory alkaloses will reduce myocardial irritability and minimize the likelihood of ventricular fibrillation. Data on changes in lung compliance during hypothermia are not available.

4. *Nevous system*—Electroencephalographic activity is reduced as body temperature falls. Figure 4 indicates that all spontaneous activity ceases at 20° C (68° F). Behavior studies in the post-hypothermic period have failed to reveal changes. Conduction along nerves is reduced and in all probability there is decreased transmission across the nerve-muscle junction. Conduction in non-hibernating animals stops at 10° C., but in hibernating ones is present as low as 2-3° C.

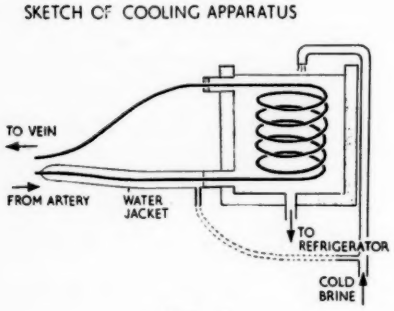
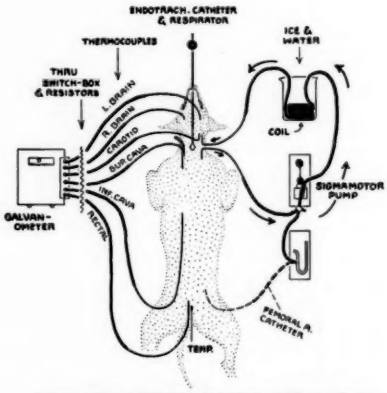


FIG. 5



Differential Hypothermia in the Dog.

FIG. 6

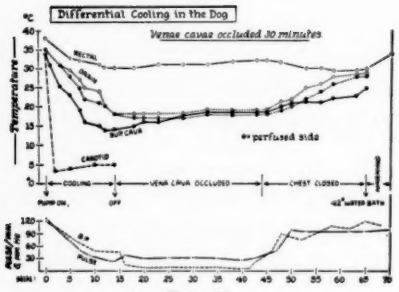


FIG. 7

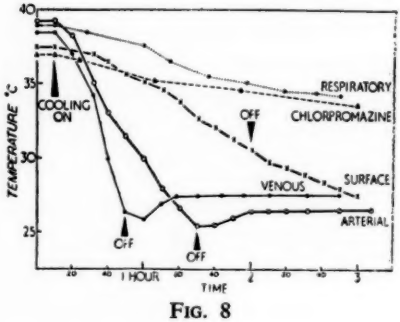


FIG. 8

5. *Stress response*—In hypothermic rats the hypothalamic—pituitary mechanism leading to the release of ACTH in response to stress stimuli is inhibited. The adrenal cortex in such cooled animals, however, remains responsive to the intravenous injection of ACTH. An inhibition of neural transmission of stress stimuli may be responsible for this block.

6. *Kidney*—At 30° C glomerular filteration rate is reduced 50 percent, but urinary output continues during anesthesia and operation on hypothermic man at a rate which cannot be ignored. The accumulation of cool urine in the bladder may interfere with rewarming unless it be removed by catheter.

7. *Blood*—Coagulability of blood decreases as its temperature is lowered, yet clinical evidence of abnormal bleeding tendencies has not been reported. Blood viscosity also increases during hypothermia. The influence of this on cardiac work has not been evaluated.

METHODS OF COOLING

Table 1 lists the common methods of cooling. External cooling of the entire body surface is commonly used. It is slower than direct cooling of the blood, but does not require cannulation of arteries or veins, nor is a pump or oxygenator needed. If an artery is cannulated, it is best to add a pump to the circuit since the heart may have insufficient force at low temperatures to circulate the cooled blood adequately. A schematic diagram of such an apparatus is shown in Figure 5.

TABLE ONE
METHODS OF COOLING

I. External (skin) Surface Cooling—whole organism
   1. Immersion—tub of ice
   2. Ice bags of plastic units containing fluid which is cooled
   3. Blankets with coils—circulating water and Prestone (ethylene glycol)
   4. Deep freeze unit

II. Internal Surface Application — part of organism
   1. Cold fluid poured into thoracic cavity
   2. Balloon in stomach containing cold fluid
   3. Cold fluid or sponges around aorta
   4. Ice water enema

III. Cooling of Blood removed from Body and Returned
   1. Artery to vein through coils immersed in cold fluid (heart acting as pump)
   2. Artery to vein through coils plus booster pump with or without simple oxygenator
   3. Vein to vein—superior vena cava to femoral vein with booster pump.
   4. Vein to artery—femoral vein to aorta at aortic valve with booster pump.

   Can be for whole body or for differential cooling.

IV. Adjuncts to Cooling
   1. Anesthesia
   2. "Curare drugs"
   3. Chlorpromazine

TABLE TWO
INDICATIONS FOR HYPOTHERMIA

1. Interruption of Blood Supply
   A. Whole Body—during "open" cardiac operations
   B. Regional
      a. Carotid artery—brain operations
      b. Descending aorta
         (1) hepatectomy
         (2) aneurysm
         (3) massive visceral excision

2. Reduce Oxygen Need in Reversible Conditions Causing Hypoxia
   A. Congenital heart disease
   B. Pulmonary, cerebral or peripheral embolus
   C. Acute pulmonary disease
   D. Anemic crises

3. Combat Hyperpyrexia
   A. Thyrotoxicosis
   B. Brain lesions
   C. Heat stroke
   D. Infections

4. Reduce "Stress"—e.g. Anesthesia, Operation
   A. Shock?
   B. "Poor risk" patients?

5. Produce Hypotension
   A. Diminsh operative blood loss
   B. Treat hypertensive crises
   C. Reduce internal hemorrhage e.g., ulcer, varices

If only a single region of the body, e.g. the brain, need be cooled, this can be achieved differentially by an approach illustrated in Figure 6. The success of such differential cooling is indicated in Figure 7 where it can be seen that brain temperature is far lower than rectal temperature. Using such a technique Jensen and co-workers[6] have been able to occlude all blood supply to the brain for periods in excess of thirty minutes with survival of the animals. The utility of this in neurosurgery is obvious when it is realized that at normal body temperatures the brain will be irreparably damaged by complete ischemia after four or five minutes. Similar methods are being applied for operations on the liver. Occlusion of the thoracic aorta high in the chest carries with it a threat of damage to the spinal cord if periods in excess of several hours are attempted.

Efforts have been made to cool the inspired gases with little success. Chlorpromazine alone has also been used in an effort to reduce body temperature. Figure 8 offers a comparision of the rates and degree of cooling achieved by various methods. It is evident that direct blood cooling is most rapid, but external surface cooling of the entire body is of value because of the greater simplicity.

Clinical Indications for Hypothermia

The uses of hypothermia have not yet been defined. Swan has recently listed a number of possibilities, some still in the realm of speculation. These are summarized in Table 2.

The ultimate role of hypothermia in surgery and medicine will depend upon its safety. If further knowledge of the functional changes attendant upon a reduction of body temperature can be translated into increased safeguards for the patient, a considerable number of indications may be developed.

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AN EVALUATION OF THE METHODS OF TREATMENT OF PORTAL HYPERTENSION

W. A. ALTEMEIER, M. D.*

Numerous surgical procedures have been developed for the treatment of patients with portal hypertension complicated by esophageal varices and gastro-intestinal hemorrhage, since 70 per cent of the patients with this latter complication die within two years under conservative treatment. Included among these procedures are omentopexy, ligation of coronary veins(splenectomy, thoracotomy for ligation of bleeding esophageal varices, ligation of splenic artery, portacaval shunt, splenorenal shunt, ligation of hepatic artery with or without ligation of splenic and left gastric arteries, and the Phemister procedure or its modifications.

As a resident at the Henry Ford Hospital, I recall helping Roy McClure do omentopexies, ligation of coronary veins, or splenectomies in patients with bleeding esophageal varices in an attempt to control or prevent hemorrhage. These procedures have been largely abandoned as a result of the recent advances in our knowledge and technical skill. It is also interesting to note that ligation of the splenic artery was first done by another Detroit surgeon, Alexander Blain, in a patient with Banti's disease and gastro-intestinal hemorrhage. This procedure resulted in necrosis of the spleen in that patient.

More recently, as the result of the studies of Whipple,[1] Blakemore,[2] Rousselot,[3] Linton,[4] Berman,[5] Reinhoff[6] and others,[7] two other methods of treatment have been developed, namely, a shunt between the portal and vena caval circulations and a reduction of the hepatic arterial blood flow and portal pressure by ligation of the hepatic artery with or without ligation of the splenic and left gastric arteries. The Phemister procedure [8] and its modifications have been reserved generally for those patients in whom shunting procedures were impossible and other forms of treatment had failed.

Since confusion still persists in many instances as to which surgical procedure is indicated for the treatment of a given case, we have attempted to analyze our experiences in 8 cases of portal hypertension and to compare the results obtained with the different operations. We have been particularly interested in a comparison of the results following the shunt procedures and arterial ligations.

MATERIAL AND METHODS

A total of 38 cases of portal hypertension have been treated surgically during the past seven years by members of the Surgical Department of the University of Cincinnati (Table I). Four cases were treated by splenectomy alone, and thirteen were subjected to venous shunt procedures. Seven of these were splenorenal, five portacaval, and one superior mesenteroportal. In three patients with severe bleeding and shock, transthoracic ligation of esophageal varices was done. The remaining eighteen were subjected to ligation of the hepatic and splenic arteries with or without ligation of the left gastric artery during the past three and a half years.

The results of therapy in these patients were studied in an effort to derive any information which would aid in assessing the value and limitations of the different procedures.

---

*Professor of Surgery and Chairman of the Department, University of Cincinnati and Cincinnati General Hospital. Presented as the Presidential Address, Henry Ford Hospital Medical Association, Detroit, Michigan, November 13, 1954.

The causes of the portal hypertension in this series were portal cirrhosis in 23 cases, post-necrotic cirrhosis in eight, hepar lobatum in one, extrahepatic venous thrombosis in five, and cirrhosis and extra-hepatic venous thrombosis in one. (Table II) The case of portal hypertension produced by congenital syphilitic hepar lobatum is apparently unique in that we have been unable to find a similar one reported.

TABLE I

PORTAL HYPERTENSION
ORIGINAL SURGICAL PROCEDURES USED

Type of Operation	Number of Cases
Thoracotomy with ligation of esophageal varices	3
Splenectomy	4
Splenorenal anastomosis	7
Portacaval anastomosis	5
Mesenterocaval anastomosis	1
Hepatic and splenic artery ligation	9
Hepatic, splenic and left gastric artery ligation	9
TOTAL	38

TABLE II

LOCATION AND CAUSE OF PORTAL BLOCK

Location of Portal Block	Number of Cases	Cause of Portal Block
Thoracotomy with ligation of esohageal varices	3	Portal cirrhosis
Splenectomy Cases:		
Extrahepatic	3	Thrombosis of portal or splenic vein
Intra and Extrahepatic	1	Cirrhosis and thrombosis of portal vein
Venous Shunt Cases:		
Intrahepatic	5	Portal cirrhosis
	5	Post-necrotic cirrhosis
	1	Hepar lobatum
Extrahepatic	2	Thrombosis portal vein
Arterial Ligation Cases:		
Intrahepatic	15	Portal cirrhosis
	3	Post-necrotic cirrhosis

The average age of the patients was 58.3 years for the thoracotomy cases, 36.7 years for the splenectomy cases, 40.5 years for those treated by shunt, and 46.7 for those treated by arterial ligation. The oldest patient was 69 and the youngest was 11 years.

All of the twenty patients treated by either thoracotomy, splenectomy, or one of the shunt procedures, had had two or more episodes of bleeding pre-operatively. In the series treated by hepatic artery ligation, thirteen patients had varying degrees of both ascites and severe gastro-intestinal hemorrhage, while four had hemorrhage only, and one had ascites only. (Table III) In general, those patients subjected to arterial ligation were obviously more seriously ill and much greater surgical risks.

Pre-operatively, each patient received a complete physical examination and routine laboratory work, as well as the following tests: blood urea nitrogen, prothrombin time, thymol turbidity, serum bilirubin, serum protein, bromsulfalien, cephalin flocculation,

and x-ray examination after barium swallow. All but five of the patients also received liver biopsies.

In the last three patients undergoing venous shunts, visualization of the portal vein immediately pre-operatively was done by intrasplenic infusion of 20 cc. of Neo-Iopax

TABLE III

INCIDENCE OF PRE-OPERATIVE HEMORRHAGE FROM ESOPHAGEAL VARICES AND OF ASCITES

Operation	Number of Cases	Pre-operative Incidence (cases) Hemorrhage Only	Ascites Only	Hemorrhage and Ascites
Thoracotomy	3	2	0	1
Splenectomy	4	3	0	1
Venous Shunt	13	10	0	3
Arterial Ligation	18	4	1	13

(70% solution) through a 19 gauge stylet needle according to the method of Leger[9] and Rousselot.[10] This proved to be quite helpful in determining the point of portal block and the selection of the surgical procedure which was indicated. Either a portacaval or splenorenal shunt could be decided upon when the block was intrahepatic and the portal and splenic veins were intact. A splenorenal shunt was performed in the presence of an obliterated portal vein but an intact splenic vein.

RESULTS

In general, the results of treatment of patients with portal hypertension are difficult to assess. The number of variable factors in a relatively small group of cases precludes any conclusions. On the other hand, several interesting observations were made in the cases treated by the various methods.

The immediate postoperative course was uncomplicated in 2 of the 38 cases.

Death occurred within three days as the result of hepatic coma and shock in all three of the patients subjected to emergency thoracotomy and suture of the bleeding esophageal varices as a desperate attempt to arrest the otherwise uncontrollable hemorrhage.

In those patients undergoing splenectomy or venous shunt procedures the immediate postoperative mortality was zero within three weeks after operation. The immediate postoperative mortality in the cases treated with hepatic and splenic arterial ligations was 11.2 per cent, however. An additional five deaths occurred among the arterial ligation cases within four and a half months, but one of these deaths was not related to the portal hypertension. Another fatality occurred in a patient who had developed recurrent bleeding 25 months after arterial ligation and who had then undergone a portacaval shunt procedure 19 months after ligation. The latter was also unsuccessful, and the patient died. A ninth death occurred in a patient in whom a portacaval shunt was done 38 months after hepatic, splenic, and left gastric arterial ligation. Hepatic failure, coma, and death occurred three and a half months after the portacaval shunt. These two patients are unique in that they are the only ones to our knowledge in whom interruption of the arterial circulation of the liver was followed by a later and secondary shunt operation. The number of deaths in the cases undergoing ligation, therefore, gives an overall mortality of 5.0 per cent for a three and a half year period after operation.

All of the seven patients subjected to a splenorenal shunt are still alive and well. Three of the five patients undergoing portacaval shunt have died, one as the result of a strangulated diaphragmatic hernia, one of recurrent gastro-intestinal hemorrhage, and one of progressive liver failure. This number of deaths in the thirteen cases treated

by venous shunt gives an overall mortality rate of 23.0 per cent.

In six of the 18 cases, 33.3 per cent, treated by arterial ligation, recurrent hemorrhage from esophageal varices has occurred. It was fatal in two and varied from minor to moderate in severity in four. In addition, generalized bleeding developed from all of the mucous membranes during hepatic coma due to liver failure in another patient, but not from the varices.

In three of the four patients who originally underwent splenectomy, recurrent and massive bleeding developed. A secondary portacaval shunt has been done successfully in one, and a Phemister procedure was performed in two when post-thrombotic obliterationtion of the portal vein prevented the completion of a portacaval shunt.

Of particular interest are the thirteen patients with both ascites and esophageal bleeding who were treated by arterial ligation. Eleven survived a postoperative period of four and a half months and none of these showed a recurrence of the ascites, and six have had no further episodes of bleeding.

Of the three patients treated by a venous shunt for ascites and hemorrhage, recurrent ascites occurred in one.

The results were poorer in the patients with post-necrotic cirrhosis who underwent hepatic arterial ligation. The mortality was high, all three patients with this lesion dying within three months of severe liver failure, while three of the four patients with post-necrotic cirrhosis treated by venous shunt have survived and have done well.

In addition to the fatal complications, others encountered were coma, protracted hypoproteinemia, atelectasis, laryngeal edema, delirium tremens, subcutaneous emphysema, and postoperative wound bleeding after heparinization.

COMMENTS

An analysis of these results has emphasized that patients with portal hypertension complicated by esophageal varices and gastro-intestinal hemorrhage are poor risk patients whose clinical problems are not confined to the hypertension within part or all of the portal bed. Severe disease of the liver may persist and may progress postoperatively to the point of invalidism or death, even though the hypertension be corrected. Hepatic coma may occur postoperatively, varices may persist, hemorrhagic tendencies from hypoprothrombonemia or thrombocytopenia may develop, or delayed or secondary thrombosis of the portacavel shunt may occur.

The poor results obtained with splenectomy alone in the four patients with extrahepatic portal blocks emphasize the recommendation that splenectomy alone should be rarely done in the treatment of portal hypertension. Instead, it is our opinion that a splenorenal venous shunt should be done at the time of splenectomy. Rousselot, Blakemore and Linton have previously stressed their belief that a splenectomy should not be done in patients with portal hypertension unless one is prepared to proceed with a splenorenal shunt. Failure to do so may result in obliteration of the splenic vein postoperatively, thereby preventing a subsequent or later splenorenal procedure. In the post splenectomy cases with post-phlebitic obliteration of the portal vein, a portacaval shunt is likewise impossible, and the surgeon is faced with the necessity of doing a more difficult and tedious superior mesenterocaval anastomosis or a Phemister procedure. It is significant to note that a Phemister operation became necessary in two of the four cases treated originally by splenectomy. Both are alive and in a fair state of health three years and one year postoperatively, although the latter has had one minor episode of recurrent hemorrhage.

In general, the results which we have obtained with the splenorenal and portacaval shunts have been superior to those obtained with hepatic and splenic arterial ligation which were done for portal hypertension with recurrent hemorrhage. The mortality rate has been considerably less, both in the immediate postoperative period and during the period of follow-up. The best results were obtained with the splenorenal shunts, all patients with this procedure being alive and well.

The anastomosis used in our cases was of the end-to-side type. It is interesting to note that the studies of Preshaw, Large, and Johnson[11] of Detroit indicate that the liver with complete shunt does not tolerate damage as well as the normal liver or the liver with partial diversion of the portal flow. They infer that the already damaged human cirrhotic liver might be further embarrassed by complete diversion of the portal blood to the vena cava, and this might be an explanation for the better results obtained in our cases treated by splenorenal anastomosis.

Although it must be remembered that the cases selected for hepatic and splenic arterial ligation were generally much greater risks than those selected for venous shunt, an immediate postoperative mortality rate of 11.2 per cent and an overall mortality rate of 50.0 per cent for the arterial ligation group is significantly higher than an immediate mortality of zero and an overall mortality of 23.0 per cent in the venous shunt group.

A recurrence of hemorrhage from esophageal or rectal varices occurred in six of the sixteen patients (37.5 per cent) surviving the immediate postoperative period of three weeks after arterial ligation, while the same complication has developed in four of thirteen patients (30.7 per cent) after venous shunting. In two of the latter four cases, however, the bleeding has been minimal and limited to small hematemesis. This suggests that the results in patients with portal hypertension and hemorrhage have been better in the patients treated by splenorenal or protacaval shunts, although it must be remembered that six patients of the original eighteen treated by arterial ligations have had no bleeding since operation 33 to 42 months ago. Considering the higher mortality rate obtained with the arterial ligation procedure, however, the operation of choice appears to be a splenorenal or portacaval shunt, particularly in the greater risk patients.

Madden[11] of New York has seriously questioned the value of ligation of the hepatic and splenic arteries in the treatment of cirrhosis of the liver complicated by hemorrhage. Eight patients were treated by arterial ligation. Four died in the immediate postoperative period, one of cardiac arrest during operation, one of massive intraperitoneal hemorrhage three hours postoperatively, one of massive hematemesis forty hours postoperatively, and one of anuria on the ninth postoperativeday. Only one of the four patients who survived operation is living, but has recurrent ascites and is in poor condition. One patient died seven months after operation and autopsy showed ruptured esophageal varices but no necrosis of the liver or spleen. One patient died three weeks after operation of hepatic insufficiency and hematemesis. Autopsy revealed no necrosis of the liver or spleen. Another patient died four months postoperatively of peritonitis. The bowl was perforated during paracentesis for recurrent ascites. A critical analysis of the results of Madden does not indicate that this procedure is not efficacious. Instead, it emphasizes the technical difficulties and dangers attending it.

McFadzean and Cook[12] in 1953 ligated the hepatic artery in five Chinese men with portal hypertension and esophageal varices. Of four patients followed, all had recurrent bleeding and two died. The operation failed to correct the hypersplenism

which all the patients had. They concluded the operation, therefore, was useless in the treatment of portal hypertension.

The value of hepatic arterial ligation in cases of ascites, however, appears possibly to be greater than that of a venous shunt. It is interesting to note that none of these patients developed recurrent ascites if they survived the postoperative period of four and a half months. This possibility needs further study for clarification. Similar promising results have been reported by Reinhoff and Woods[13] in the treatment of ascites.

The high mortality rate obtained in our cases of post-necrotic cirrhosis treated by hepatic artery ligation suggests that this procedure is too hazardous for this condition.[14] The development of severe and fatal liver insufficiency three to five weeks postoperatively with coma, shock, massive ascites, uremia, generalized bleeding from all mucous surfaces and terminal pneumonia is a complication which will preclude the use of hepatic artery ligation in our cases of post-necrotic cirrhosis in the future.

The value of excellent medical assistance in the diagnosis and treatment of these patients cannot be over-emphasized.

SUMMARY

On the basis of this study of surgically treated cases of portal hypertension, the operative formation of a venous shunt between the portal vein and the vena cava or the splenic and renal veins, is the most satisfactory and safest procedure for the treatment of recurrent hemorrhage from esophageal varices. Patients with severe and advanced cirrhosis were greater surgical risks than those with extrahepatic blocks.

The splenorenal shunt has given the best results in our hands. Hepatic and splenic arterial ligation has given irregular results in patients with portal hypertension and hemorrhage, the results being good in only one-third of the cases. The higher overall mortality rate obtained with the arterial ligation procedure has made it more dangerous than the venous shunt. Since a very high mortality rate occurred in patients with post-necrotic cirrhosis who were subjected to hepatic arterial ligation, this condition should probably be considered a contra-indication for this operation.

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NUTRITION AND INFECTION

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Before the advent of chemotherapy and the antibiotics, the physician's efforts were directed largely toward supporting nature's own response to an infecting agent, and he came to realize early that the success of this reaction to disease was determined well in advance of his intervention by the composition of the tissue with which he had to deal. An analogous situation existed in the attempts to repair water and electrolyte losses in the diarrhoeal states. About thirty years ago, after Gamble's brilliant work had given us some confidence in the use of parenteral fluids, I analyzed the mortality figures in an infants' hospital for ten years that preceded and two that followed the introduction of his ideas. The patients came from the lowest economic circumstance and had obviously been malnourished before the acute episode that occasioned their admission. In spite of our seemingly more intelligent management of fluids, we had effected no change in mortality; we were still losing approximately 240 patients per thousand admissions. In studying the past histories of the fatal cases, it was obvious that the summer diarrhoeal episode to which we were attributing death was merely the final chapter in a chronic disturbance of nutrition that had produced what has been termed "metabolic bankruptcy." Something was missing which made impossible the reconstitution of normal tissue, and which could frequently be predicted from the determination of the serum proteins. The changed picture in this group has not been the result of either anti-biotics or of more refined calculations of electrolyte losses, but of greater appreciation of the nutritional requirements for growth, qualitatively and quantitatively. The diarrhoeal problem is still with us, but when it occurs in infants adequately fed before the episode, it no longer contributes prominently to mortality, save in sporadic outbreaks in the newborn.

In tuberculosis, the brilliant contribution of streptomycin, isoniazid, and PAS may have made us forget a few hard-won facts about the role of nutrition in the development and course of this disease. In a twenty-five year study of 1100 reactors removed from contact, we felt that we were able to demonstrate that endogenous reinfection does occur; that a literal "breaking-down" could be referred to a failure of nutrition; and that subsequent healing paralleled more than any one thing the adequacy of the nutritional state as reflected in the storage of nitrogen.[1] This was not the simple problem of providing a good diet, but involved rather a careful consideration of a host of factors influencing favorably or otherwise the retention of ingested materials—infectious, glandular and emotional.

Rheumatic fever is conceded to be a disease state occurring preponderantly in the lower economic strata. For its development there would seem to be three factors involved—the infectious agent, usually a streptococcus; an inherited predisposition, which probably describes a sensitivity state; and a conditioning factor, seemingly associated with something present in the lower economic strata and not so frequently found in the upper. The first two of these factors would be common to all economic levels. In considering the third, it is difficult to dissociate items such as housing, clothing, dampness and diet, though the intake of dairy products and animal protein will be found consistently to fall with income. The literature that would incriminate nutritional defects as playing a prominent role in the outcome of rheumatic fever is impossible to ignore.

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Read before the A.M.A. Section of Pediatrics, Miami, Fla., Nov. 29, 1954.

In Coburn and Moore's[2] thoughtfully evaluated study, the only question arising had to do with the particular items that were most significantly absent from the diets, since protein, calcium, iron and Vitamin D were all a suspected group. It was of particular interest that in fourteen children from wealthy families only one could be said to have had a good diet; in ten, eggs were absent from the diet, sometimes because the children disliked them, sometimes because they were considered to be allergic to them. In the study of Warner and Winterton,[3] a low intake of milk seemed the most prominent item. As they reported, to quote them, "Perhaps the most striking fact suggesting that an increase in animal fat in the form of fresh milk and butter may be of prophylactic value is furnished by the figures from Christ's Hospital where the incidence of rheumatism was reduced to less than a third corresponding to a rise in the animal fat consumption from 50.6 grams to 103.6 grams, due largely to an increase in the rations of milk and butter." The increase in milk involved, of course, increase in protein and calcium which could hardly be ignored. Wallis[4] has recently offered an interesting comment on the possible value of egg. In analyzing the diet habits of a significantly large number of rheumatics and controls, he found that 40 percent of the cardiacs ate few eggs in contrast to 16 percent of the controls. There was active dislike of eggs in 10 percent of cardiacs compared to 4.6 percent of the controls. He points out that the inhibitor of hemolytic activity of Streptolysis S-9 produced by group A streptococcus depends in part on serium phospholipid, one of whose ingredients is choline, a substance which can be neither synthesized nor stored in significant amounts. Eggs would provide an excellent source of it. I realize that there is constantly quoted the experience from the armed forces of the relatively high incidence of rheumatic fever among service men, though their diet was the same as those who remained free from the disease. On this, I would point out three things: (1) The composition of the tissue of these men was determined years in advance of their entrance into service, (2) the role of nutrition in rheumatic fever is less one of influencing incidence than of influencing final out come, and (3) in our tuberculosis work we found that the perfect diet might be offered, but in the case of protein, only one adolescent out of three took this by choice if the preference for carbohydrate had been established by the dietary pattern at home.

In an attempt to evaluate the effect of cortisone in rheumatic fever during the past five years, I recently analyzed for control purposes, my own experience over a twenty-year period preceding the use of this hormone. The case material is derived from a clinic serving for the most part the middle economic stratum. My experience prior to this had been limited to three large teaching institutions serving the indigent, the type of patient dealt with in the best available follow-up study of rheumatic fever. Although my follow-up has not been nearly so long (a mean of 66.6 months per patient for those seen before 1938, with 27 followed for longer than 108 months, and a mean of 50.6 months for those seen between 1938 and 1949, when cortisone was started), the results are sufficiently contrasting to quote them:

OUTCOME IN RHEUMATIC FEVER

	Boston Study[5]. 1000 20 years	H.F.H Study 218 8 years
No carditis	10.8%	27%
Carditis with no functional handicap	31.6%	44.4%
Carditis with functional handicap	17.5%	22.4%
Death	30.1%	6.4%

That rheumatic fever could and did occur in the better economic groups was evident, but the difference in the end results was impressive. In attempting to assess the relationship between nutrition and outcome, a plotting of the patients on the Wetzel grid was used as a rough appraisal of the former. I would accept the criticism that weight does not measure nutrition, but the correlation is high when extremes are considered. In the study, Wetzel's[6] three central channels are used as "average;" his upper three as "above average;" and the lowest three as "below average." The first two categories are grouped as "good," the third as "poor." For purposes of a contingency table, a good outcome was considered to be the failure to develop carditis or signs of a carditis with no functional handicap; a poor result was considered to be a functionally handicapped child or a fatal outcome. A distribution curve skewed to the left would describe a group weighed as above average; to the right as below average. The correlation between outcome and nutrition as measured in this way proved highly significant.

It would be premature to place on record the outcome in the cortisone-treated cases, of whom we have had 82. The point is made here, however, that when that evaluation is made it must take into account the nutritional state of the patients studied as a factor conditioning outcome in advance.

In conclusion, I would stress my feeling that when a pediatrician is able to influence favorably the nutritional state, he is probably making a contribution to the entire life history of the response to infection. But I would point out further that this is not merely a problem of providing an adequate diet, but of carefully considering all of those factors which affect its utilization.

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PRESENTING THE DIAGNOSIS OF FUNCTIONAL ILLNESS

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In lecturing recently to medical residents on "Psychotherapy", I said among other things that when the doctor considers the patient's primary disorder to be an emotional illness, he should so inform the patient honestly. Later, I read an article by Hart[1], who writes: "There is no evidence to show that patients with cardiac neurosis really fear heart disease; on the contrary, their over-all behavior suggests that they need and seek a tangible organic defect, perhaps as a rationalistic lesser-evil defense against suspected mental illness. In these patients, reassurance that the heart is sound is not only ineffective but commonly aggravates anxiety and other symptoms." Hart does not tell the patient his honest opinion that heart disease is absent, but instead ". . . hasty diagnoses were frowningly deplored, and a truthful, but indefinite statement was made: 'I don't know yet what the whole trouble is.' " Return visits were made, keeping the emphasis on re-examination, on physical complaints, on avoidance of probing into personality factors, and in exhibiting "genuine human interest in the patient as a person."

Hart's statement and his technique are at variance with the procedure which I, a psychiatrist, had advocated; yet I could see that his position is sound. Perhaps there is some truth in what each of us in saying, and our difference occurs because our viewpoints reflect our different specialties.

Hart is talking about what we psychiatrists call "resistance." In all psychotherapy, interpretations (truth as the doctor sees it) may be misunderstood and rejected by the patient, often with resentment—not because the interpretations are incorrect but simply because, as the layman says, the truth hurts. Judgment is required to determine how rapidly to give the interpretations, and how to give them with the least discomfort to the patient. It is better that he learn a little of the truth which he can accept and use constructively, than that he hear it all and accept none of it. Nevertheless, however cautiously, slowly, gently we approach the patient's resistances, it is still our task to approach them, test them, to keep trying patiently to tell him a little more of the truth (as we see it) about himself.

If I have failed to apply this knowledge I already had about the general subject of resistance to the question of how a diagnosis of functional disease is to be presented to the patient, it is because I did not realize how strong a resistance patients in general have to that diagnosis. This came about because of two features of my specialized position as psychiatrist:

1. When the patient comes to the psychiatrist, the mere fact that he is there at all is an indication that he has already partially accepted the idea of emotional causation of his disorder. The fact of his being there may well represent a good deal of effort and explanation and persuasion on the part of the internist who sent him.
2. The internist, not the psychiatrist, bears the responsibility if perchance his opinion that no physical disease is present is later found to be wrong. If the internist has in addition expressed an opinion that the cause of the symptoms is in the emotional life, the patient will be doubly bitter, for he will think that the doctor added insult (by calling it psychogenic) to the injury (of overlooking the physical disease). Such experiences, from which the psychiatrist is largely spared, teach the internist first-hand to have great respect for the patient's resistance to the suggestion that his illness is emotional.

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There is then good reason for the diagnostician to approach that resistance gingerly. I consider the technique Dr. Hart uses, that of giving the patient a "truthful but indefinite" answer, to be all right—as far as it goes. However, I would dislike to think that it is as far as the internist can and should go with the majority of his patients. Most patients can accept a little more of the truth than that; furthermore, they will press the doctor, after the first two or three visits, for more definiteness in diagnosis. The technique I was advocating is at the opposite end of the scale from Hart's technique, and I now see it is too blunt for the internist to use, at least just as soon as the diagnostic studies are completed. There are, however, some in-between stages which can be listed. I believe it is the duty of the internist to choose how far along these in-between stages he should conduct each particular patient—depending both on his opinion of the patient's needs and the patient's capacity to accept these successive fragments of the truth. If the patient needs and can take it, the doctor should no more flinch from the unpleasantness of giving it than he flinches from giving a painful injection which the patient needs and can take. In general, the unpleasantness can be largely avoided if the doctor merely waits until the patient himself brings up the next fragment of the truth, and the doctor merely affirms it.

One may begin where Hart does: I don't know yet what the whole cause of your symptoms is; next, the cause of your symptoms is malfunctioning of certain organs; then, the malfunctioning is caused by nervous or emotional tension; then, nervous tension is caused by poor mental and physical hygiene, and/or current stressful life situations, and/or unfortunate circumstances in your past life over which you had no control. If the internist does carry the patient successfully to this point of self-knowledge, he will have attained all I had in mind originally, in advocating that the doctor honestly inform the patient of his opinion that the primary disorder is an emotional illness.

It is beyond the province of the internist to go into the reasons, the causes for these things: the patient's apparent inability to correct his poor mental and physical hygiene by resolving to do (i.e., to learn how to relax and to follow good health rules); the patient's apparent inability to correct his current life stresses, to escape from them, or to tolerate them with equanimity; and the fact that the patient himself has played some part in creating both the past and present unfortunate circumstances of his life. In general, the reason for these things lies in the fact that his behavior, which is now so troublesome to him, once had a useful purpose. He once "wanted" to behave in a somewhat similar way to gain an emotional satisfaction (such as the love of his mother); and now when he cannot find, on the adult level, adequate emotional satisfaction, he regresses to behaviour which gives him, on an immature level, a somewhat similar substitute satisfaction. In short, there is still a part of him which "wants" to behave as he does. We might say, the trouble with us is ourselves. This is a nice phrase anyone can readily apply to himself—in general; but the resistance is so great when we start applying it in particular, that an entire medical specialty, Psychiatry, has had to arise to try to deal with it.

SUMMARY—If your opinion is that the patient has no serious physical disease, and his disorder is primarily emotional, you need not immediately tell him these opinions fully and frankly. Many patients have a strong resistance to accepting these particular opinions, and it is better to tell him a little of the truth which he can accept, than all of it which he cannot accept.

A number of means of disclosing these opinions partially, in a step by step manner, are mentioned.

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ASTHMA IN CHILDREN

THADDEUS H. JOOS, M.D.,* AND ROBERT S. ELLIS, M.D.**

The material comprising this paper represents the follow-up on 100 patients under 12 years of age who were first seen during the years 1934 to 1940, and who were treated mainly by allergic cleanliness, and hyposensitization measures. These patients were followed for from 3 years to 10 years. In the series there were 60 males and 40 females. The average age of onset of the asthmatic symptoms was 4.4 years of age. There was a family history of asthma in 68 children and the same number had some associated form of allergy such as eczema, urticaria, or hayfever.

An additional twenty children are also included who had been poorly controlled on the standard anti-asthma programs. These patients were treated in the clinic in 1953 and 1954 with "Tyral," a preparation containing 200 mg. of the amino acid tyrosine, 2.5 mg. of pyridoxine HCL, and 10 mg. of niacinamide. The purpose of this compound is to supply the body with ample precursors of adrenalin. Tyrosine is the amino acid from which adrenalin is made; pyridoxine acts as a co-enzyme in its build-up; and niacinamide is employed for its anti-histaminic action. The dosage was three "Tyral" tablets four times a day.

PATHOLOGY

In the allergic state there seems to be one organ that is susceptible to the insult of a histamine response to an antigen. Be it the skin as seen in eczema and urticaria, or the respiratory system, as in asthma where we see edema of the bronchial mucosa, spasm of the smooth muscle of the bronchial tree and mucous plugs in the bronchioles, the pathologic processes are similar.

The reasons for the particular responses seen in the allergic state are still obscure. Perhaps such experiences as infections or emotional trauma lower the susceptibility of the response organ and the clinical picture is produced. Another interesting concept has been brought out by Widmann and Keye[1] who theorize that the allergic individual has a low circulating adrenalin which makes possible the appearance of the signs of allergy. Much work is needed in an effort to help us understand the exact mechanism behind the allergic response.

CAUSE

The etiologic allergens in childhood asthma are for the most part inhalants, although food sensitivities do play some role.[2,3,4,6] Endocrine imbalance has long been recognized as a factor in allergy, and this was borne out by the children in our series who exhibited hypothyroidism as manifested by delayed bone age and/or low basal metabolic rates. Emotional causes are hard to evaluate, but one could not help seeing in some cases clear-cut evidence, despite specific sensitivities, of perhaps "psychic sensitivities" which played major parts in the child's asthma pattern.

In the determination of the specific causative allergens, history was most important, and skin tests were often used to support the material gained from the history. The skin testing material was prepared after the method of Coca,[6] and the usual skin test dose was 0.1 cc. of a 1:100,000 or 1:10,000 mixture given intradermally. Chart number 1 shows

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the number of reactions seen in the group of 100. For a reaction to be considered significant 2+ reading had to be obtained. Not only was the skin test reaction helpful in the determination of the causative allergens, but it was also useful as a guide to the initial hyposensitizing dose. An example is the child who responds 4+ to a 1:100,000 ragweed injection and has mild asthmatic symptoms caused by this test dose. He needs a very small starting dose, such as .05 cc. of a 1:1,000,000 dilution, so as to avoid systemic reactions.

CHART No. I

Allergen	*Reactions*
Bacteria	83
Grasses	53
Ragweed	53
Foods	31
Dusts	26
Danders	16

Bacterial sensitivity can be seen to be the principal cause of asthma in childhood and by history, 44 of the patients had an attack provoked by an upper respiratory, tonsil, or sinus infection. The reverse was also often true, that control of the infection brought an end to the asthma.

TREATMENT

The therapy of the chronic asthmatic should be divided into immediate and long range management[7,8,9,10].

IMMEDIATE: For the control of an acute asthmatic episode there are of course the standard and time-proven preparations employing adrenalin or a related compound, aminophyllin, an iodide, and a sedative. A particularly useful solution in refractive cases was found to be one composed of 100 to 200 cubic centimeters of 5 per cent glucose in water, 250 to 500 milligrams of aminophyllin, and 20 to 40 cubic centimeters of a 10 per cent sodium chloride solution. This mixture was given intravenously over a 30-90 minute period and produced excellent results in almost every instance.

LONG RANGE: The long range program should include several steps:

1. *Allergic cleanliness*—These measures include removing a serious focus of infection, such as an infected maxillary antrum. Good anti-dust or dander campaigns in the home are needed. Elimination of specific foods, when found to be harmful, is in order. A word of caution, however, should be introduced regarding the elimination of essentials. Too often an individual goes into a state of nutritional bankruptcy on a rigid elimination program, thereby making a favorable response to any stress situation, including allergy, nearly impossible.
2. *Correction of Endocrine Inbalance*—If the hypothyroid state exists correction of course is mandatory. In our eight hypothyroid children the addition of thyroid extract to the anti-asthma regime brought gratifying results rather promptly in six of them.
3. *Vaccines*—The hyposensitization with the extracts that gave positive skin reactions has long been used. We employed this method in eighty-eight of our children and obtained good results in fifty-one of them, or 61 percent. Good results meant at least a 50 percent improvement in the signs and symptoms.
4. *Psychological Care*—The "psychic sensitivities" of course should be investigated

wherever possible, but often this therapeutic approach is disappointing. Correction along these lines includes not only counselling of the patient but also of the parents.

5. *Tyral*—As mentioned previously, a small number of childhood asthmatics were placed on this medication alone. With this compound we hoped to provide the children with a maximum of the necessary materials used in the synthesis of adrenalin by the body. The work of Widman and Keye[1], plus that of Woodward[11], and also Spickard[12] gave good results in 75 percent of asthmatics in the pediatric age group. Some of our results have been in accord with theirs, being classified by parents as "miracles." On the other hand the exact opposites were encountered, meaning dismal failure using Tyral and/or purified tyrosine[13].

While the final results present a somewhat hazy picture, this new drug may in the end, provide us with one more effective agent to treat the chronic asthmatic.

DISCUSSION

At first glance, the prospect in the long run for childhood asthmatics may appear to be poor, but this certainly is not true. We can see that with vigorous treatment including hyposensitization measures, six out of ten chronic asthmatics can be controlled. This figure is certainly in keeping with that of Rachemann and Edwards[8], who reported a twenty-year follow-up on 449 childhood asthmatics. They gave the encouraging figure of 71 per cent being asthma-free after twenty years, provided adequate therapy was given. The key, therefore, to good asthma management is to find the causative factors, if possible, and then proceed to treat these children in an energetic fashion.

SUMMARY

1. 100 cases of asthma in children are reviewed.
2. The exact mechanism behind the allergic response is still obscure.
3. Inhalants, including bacteria, grasses, ragweed, were the most frequent allergens noted, with foods, dusts, and danders next in importance.
4. Emotional causes are prominent in some cases.
5. Immediate treatment is usually not controversial.
6. Long term treatment can be successful, but each case must be individualized as to the methods to be employed.
7. In our hands, therapy including hyposensitization procedures gave 61 per cent favorable long term results.

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FLORENCE NIGHTINGALE AND ONE HUNDRED YEARS OF MODERN NURSING

Twenty-Eighth Commencement — 1954
H.F.H. School of Nursing

FRANK R. MENAGH, M.D.*

When Miss Moran invited me to address the 1954 Graduating Class of the Henry Ford Hospital School of Nursing, I accepted the assignment with great pleasure, marred only slightly by the added remark, doubtless much appreciated by you, that I was at liberty to roam at will in the one hundred-year history of modern nursing, just so long as I did not take more than twenty-five minutes in which to do my roaming. However, I can assure you that it gives me much satisfaction, a real thrill, to appear before this splendid group of professionally trained young women. And this is not only because you in yourselves represent so much solid accomplishment and are such an invaluable part of the professional assets of the community, but because you are also true representatives of the twenty-seven classes that have graduated before you from our own School of Nursing. Representatives of those splendid women who have received similar training in the last one hundred years, and splendid women they were, too. I know. I married one of them!

You represent, as well, the most respected of the professions today. So convinced is the public of your technical competence and your personal integrity that any criticism of nurses comes as a great shock, and there are not many such made. One of the first lessons that I learned as a young physician was that when a patient, usually, but not always a woman, starts off an interview by telling me with great pride that she has a friend who is a trained nurse and that this nurse had told her so and so, never to question the information so given. To do so would throw suspicion on my own qualifications. I always start with such statements as the law and gospel and when I reach my own conclusions, I make them sound as much like those of her friend, the nurse, as possible.

But you represent even more than this. Your profession has been the spearhead of the most beneficial development of the last one hundred years, the liberation of women from the role of purely domestic servants to a wider sphere, outside the home, where their intelligence, energy and special talents have been released for greater service to society. Nurses are not the only group of trained women, but they were the pioneers and, together with the teachers, form the largest and most valuable group of professionally trained women today. And I might add that so far as I can see, their role as home-makers has not suffered; in fact, it has been improved. This change has not come without great effort. Even as late as my own school days, the women who took up nursing were thought to be exceptionally courageous, though there was never any question as to their moral or intellectual status. But the amazing thing about this change, so far as the nurses are concerned, is that the pattern of service and behavior of this notable group was not a matter of gradual development but was fixed from the start by one remarkable woman who used as her pattern her own abilities and convictions. It is truly astounding how much of Florence Nightinagle we can see in this Class of 1954.

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At this point you may well ask, why talk again about Florence Nightingale, and if she was to be selected for our subject, why was I selected as the speaker? It is almost as though I had been asked to talk about flower arrangements. To answer the second question first, my only qualifications are my great admiration for the woman herself and a lively sense of respect for her accomplishments. And again why talk about her? The fact is that she is one of those really great people who are most appreciated when you know the most about them. She has much in common with Abraham Lincoln. The speeches and articles on Lincoln today show a far greater understanding of the man and his worth than did those of his partisans of an earlier day. It is not too easy to grasp the genius of Florence Nightingale. Every time that I have gone back to study her I have come away with a different impression. The woman grows on you. It seems that there are three stages in interpreting her. The first might be called the saccharine stage. This is the period when you think of her as the lady with the lamp, going her rounds, meek and gentle, giving aid and succor to the sick and wounded. This was the popular heroine, and, indeed, she was this too. And then, secondly, there comes a realization of her tremendous power and tenacity in gaining her objectives. Here the emphasis is on what she herself called her "Battering Ram" characteristics. This side of the picture is so forceful that you forget her other qualities. And finally with further acquaintance, you realize that here is no ordinary person at all and that all of her history and activities must be studied. Each time that you go over this material or parts of it, new facets of her personality emerge. She becomes a true genius.

Florence Nightingale was born in 1820 and lived to be ninety years old. During most of this time the "stuffed shirt" reigned supreme and this stuffed shirt as often as not surmounted petticoats. By a "stuffed shirt" we mean persons with fixed opinions, guided solely by precedent and social custom, indifferent or hostile to the introduction of new facts and of any interpretation of these facts that might upset their preconceived notions. Such persons are apt to be in the higher echelons of society and government and are accustomed to having their prejudices treated with respect. Florence Nightingale took them all on — first in the domestic circle, then in the leading social circles of her day, then in the Army, the worst of all and, finally, in the government. Red tape had for her no terrors and she knew how to use it for her own advantage. By the sheer power of her mental capacity and her persistence she was able to greatly accelerate toward purely liberal attitudes those forces that were already present. She was not a person who was ahead of her times; she was just in time to lead a popular movement and to give to it a desirable character. Good timing, in fact, played a large part in her success.

If any further apology is needed for talking about Florence Nightingale, the fact that 1954 is the one hundredth anniversary of the British entry into the Crimean War could be cited.

Florence Nightingale was born in Florence, Italy, and was named for the city of her birth. It may be prophetic that she was so named because up to that time, and for thirty years afterwards, Florence was a masculine name but so many girl babies were named after her that the name came to be wholely feminine in English-speaking countries. A few years before you young women were born, the biggest theatrical production each year was the Ziegfeld Follies, produced by a fine showman named Florenz Ziegfeld, born, I believe, in Austria. He had as his leading lady a very fine actress and musical comedy star, Billie Burke. In due course of time they decided to marry and once this

decision was reached they lost no time. They procured a license and presented themselves before a minister who had never heard of either of them. The minister learned that their names were Flo and Billie, but the ceremony had to be stopped and explanations made when the minister persisted in trying to get Billie Ziegfeld to take as his lawfully wedded wife Flo Burke.

The Nightingale family was wealthy, very intelligent, and moved in the best of English society. They had only two children, both girls, and these were brought up in the standards of their social level. In those days all gentlewomen were pure and chaste because their families saw to it that they never had a chance to be anything else. Everybody, including the gentlewomen themselves, subscribed to the rather insulting proposition that if they were allowed to rub elbows with the world they would very shortly cease to be gentlewomen. Perhaps this is where the opposite concept of "wild women" originated. At any rate these girls lived very sheltered lives. They were, however, widely travelled, lived much in Paris and Italy, and spoke the European languages like natives. Florence proved to have an unusually keen mind and a restless one that must always be at work on something. She became an excellent Latin and Greek scholar, was widely read in history, and followed closely the economic and political problems of her day. In fact she knew many of the people who were engaged in the various European revolutions of that time. She also was an excellent mathematician, much to the distress of the family, as this was supposed to be outside of a gentlewoman's sphere of interest. She had a flare for statistics, was always compiling them, and learned to use them effectively.

When she was about sixteen years old, she felt that she had had a divine call to do some kind of work. What the work was to be she did not know but she was not then interested in nursing. During this period she carried on the normal social activities of her family. Her father and uncle engaged an entire floor of the Carlton Hotel for the London season during the coronation of Queen Victoria. She had an adequate number of beaux, kept them dangling as long as possible and then said, "No." She apparently never had the least intention of marrying. She was interested in the welfare of the common people, an interest that her friends found it hard to understand. Gentlewomen were not supposed to be interested in workmen and their families. She was well trained in philosophy and, realizing the popular religions of her day did not too successfully meet the needs of the intelligent artisans, she devised a religion, within the framework of Christianity, that would appeal to them. She tried writing but did not like it. In her late twenties she fixed on nursing as her great objective. She did not even dare to mention this to her family at first, and when she did do so there was a storm. Her sister had a nervous breakdown because of the shock. But Florence Nightingale was no rebel. She didn't renounce her family and its advice. She just kept boring ahead. Finally in her early thirties she was allowed to take some instruction in the best hospitals of Germany, France, and England. And at long last after years of ceaseless opposition from her family, she was installed as the superintendent of a small nursing home called "An Establishment for Gentlewomen During Illness." It was of course not adequate for her plans which she had now crystallized. Her goal was to train young women as nurses and to teach society that such training was a proper vocation for nice women and that they should be accepted at their true worth—two very difficult objectives, especially the latter. She was now thirty-four years old and the year was

1854. This was the year Britain entered the Crimean War and the year of the great opportunity for Florence Nightingale.

There will not be time enough today for us to refight the Crimean War. There has been a new book on the subject, just published, called "The Reason Why" by Cecil Woodham-Smith. The author is a woman who has emulated Florence Nightingale by being christened with a boy's name. Appropriately enough, she published in 1951 a life of Florence Nightingale. It is interesting to note that she spent eight years working on the Nightingale papers and then followed largely the classical biography of Sir Edward Cook.

Those of you who may be a little vague as to the geography of the Mediterranean basin will find a very interesting half-hour in going over this area in an atlas. It is about 2500 miles from the Straits of Gibralter to the eastern end of the Mediterranean Sea at modern Israel. To the north long fingers of water reach out to Southern France, Italy, the Adriatic and the Aegean Seas. From the upper end of the Aegean Sea, the Dardanelles lead to the Sea of Marmara and across this to the Bosporus, opening out on the Black Sea. On the European side is Istanbul or Constantinople. Across the narrow strait is the suburb of Scutari. About 300 miles further east, hanging like a pear from the north shore of the Black Sea is Crimea, practically an island. On the southern point of Crimea is Sevastopol, where the Russians had built a strong naval base with the idea of opening up the straits and so giving Russia an unhampered warm water port. When the British entered the war in 1854, the object was to capture and destroy Sevastopol. The base for the care of their sick and wounded was at Scutari, 300 miles to the west.

The Allies invaded Crimea on September 14th and the battle of the Alma was fought on September 20th. It was a hard-won victory. The losses were heavy and in addition to the wounded, cholera had added to the number of the sick. No adequate preparations had been made for the care of these men and by the time they reached Scutari their condition defied description. They had no clothing, no food, no medicine and few Medical Officers to care for them although the Army had one Medical Officer to each ninety-five men. There were supplies but they were always in the wrong place. Forty-two percent of the men who lived to reach a hospital died. So far as the care of the sick and wounded was concerned, it was a thoroughly bungled job. And yet the men and equipment were there and, given enough time, they would probably have muddled through somehow. However, the British Army had a new departure from the past wars in that the London Times had sent out its own Special Correspondent, one William Howard Russell. While not welcomed by the Army, he seems to have been given a free hand. While England was still wild with excitement over the great victory of the Alma, Russell's dispatches began to arrive telling of the condition of the sick and wounded. He was a man capable of high indignation and his stories told the exact truth. England was horrified and there was a great public demand that something be done at once. In his dispatches Russell noted that the French soldiers were much better cared for than were the British, and he noted that the nursing sisters who were with the French Army were in part responsible for this. Why could not the British have some similar service?

Russell's dispatches arrived in London on October 9th, 12th and 13th. Among others, two persons of importance read these dispatches with special interest. One was

Florence Nightingale in her little Establishment for Gentlewomen During Illness, and the other was a friend of hers of many years, Mr. (afterwards Sir) Sidney Herbert, Minister of War, and the man in the Ministry who was responsible for supplying the Army. Miss Nightingale wrote to him on October 14th saying that she would be willing to head such a nursing Corps, provided her family would consent, etc. On October 15th, Sidney Herbert wrote to Miss Nightingale asking her to do just that. The letters crossed. Six days later on October 21st, Florence Nightingale and her party of nurses left London. She had promptly seized this golden opportunity to establish nursing in the minds of people generally as a respectable and valuable profession.

The most difficult detail in arranging this expedition was the selection of the nurses who were to be taken. One of the reasons that Florence Nightingale's family had objected so strenuously to her entering nursing as a career was the low esteem in which nurses generally were held. And not without some reason. The best of the nurses, both from the point of view of morals and training, were the nursing sisterhoods. The trouble here was that there were not enough of them and that their religious intolerance made it very difficult to weld them into one organization. The hospital nurses outside of the sisterhoods were in general a hard lot. It was taken for granted that all nurses were addicted to alcohol; in fact, it was thought that they could not carry out their difficult work without it. The average hospital nurse was not trained at all in the usual sense and only took up this work because she was fit for no other. It was decided to take no young women as nurses and it was with difficulty that thirty-eight were finally selected who would go and who seemed likely to prove useful. Strict regulations were issued as to their conduct. For one thing the amount of alcohol that they were to receive was limited. They were to get a pint of ale or bitters with their dinners, and half a pint of the same or an ounce of brandy with supper. Later from Scutari, Florence wrote back home that "fat drunken old dames of 14 stone and over must be barred, the provision of bedsteads is not strong enough." Even so, many had to be sent home because of drunkenness, including several of the Presbyterian nurses who had been sent out to equalize the religious representation. With the exception of the sisterhoods, who wore their habits, all the nurses must wear the same uniform. This uniform appears to have been selected, not to set off the grace and allure of its wearer, but quite the reverse. It had the advantage of easy identification at distances up to one mile and like the classical uniform of a recruit, it didn't fit. One of the nuns wrote, "That a 'lady' could be induced to appear in such a get-up was certainly a triumph of grace over nature."

The party left London on the 21st of October and sailed from Marseilles on October 27th. They sailed in the *Vectis,* an old mail-ship that was so uncomfortable and hard to handle that the Government had trouble recruiting crews to man her. The second day out, a good Mediterranean gale hit her astern and blew her across the 2000-mile journey in record time. They had to jettison her guns, and the steward's cabin and the galley, built like small garages and bolted to the main deck as was the custom in the old sailing ships, washed overboard. But on she went, up the Aegean Sea, through the Dardanelles and across the Sea of Marmara to the Bosporus where she dropped anchor in front of Scutari, seven days out of Marseilles, including a one-day stop at Malta. It was a fast trip and they arrived on November 4th. The timing was again just right and the next day, November 5th, the battle of Inkerman was fought.

Again, the wounded in horrible condition flooded in. Things were still very difficult but the new nursing corps was given a chance to prove themselves. That they did succeed is a matter of history. But that they succeeded because Florence Nightingale was a great administrator, a fine quartermaster, a diplomat and a skillful politician, as well as a sympathetic and skillful nurse, is not so well understood. She herself contracted the Crimean Fever and nearly died but she never deserted the Army and she made her Nursing Corps an accepted and respected organization.

When she returned to England in 1856, she was a national heroine. Books, pamphlets and imaginary pictures of her (she never released her own photograph) were published. Ships were named for her and, as we have noted, so many girl babies were named Florence that it is still a popular feminine name. They even named a race-horse for her and this filly, unlike most horses named for prominent persons, proved to be a good one and the newspapers carried the announcement that Miss Nightingale had won the Forest Plate Handicap over, appropriately enough, Barbarity and nine others. And I suspect that she rather liked that, as she was an accomplished horsewoman.

Her influence in England was tremendous. She was the friend of royalty and the master of Ministers in the Government. A threat to appeal to the people usually won her point for her. She lived for fifty-four years after her return to England and whether it was the result of keen psychology or by accident, her decision to withdraw from the public eye increased and prolonged her influence. She spent most of the rest of her life in bed but did a tremendous amount of work. Her greatest contributions came during this period. She established her training school for nurses, and the first graduates of St. Thomas would compare well in training and character with you who are graduating today. Beyond this, her work and interest were largely in what we today would call the field of Public Health, but the welfare of the enlisted men in the British army was always close to her heart.

If Florence Nightingale were alive today and had sent to you a personal message on the event of your graduation, I wonder what she would have said. It might be that she would repeat two bits of advice that she had previously given to nurses. First, to gain the greatest satisfaction from the training that you have had and in the work that you will do, you will need first of all a sense of devotion. May I quote, "I use the word in a very wide sense, meaning that state of mind in which the current of desire is flowing toward one high end. This does not presume knowledge but very soon attains it." And second, use the fine training that you have received to introduce into your own life an ordered pattern of living. With these two precepts, life should bring you much satisfaction.

THE ARTERY BANK

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One of the most noteworthy achievements of surgery in recent years has been the treatment by resection and grafting of vascular lesions of grave import formerly regarded as unsuited for such direct approach. First chronologically, if perhaps not in practical importance, was the successful accomplishment of the cure of coarctation of the aorta by resection and grafting. Through lessons learned from angiography it has been established that peripheral arteriosclerotic occlusive disease is often segmental in its distribution and that lesions of this type are amenable to excisional and grafting procedures. Aneurysmal disease of the aorta and of the large vessels have likewise been found to be manageable by resectional treatment. Graft replacement, on the stimulus of its successes in the handling of chronic degenerative lesions, has come into wider use also in the care of acute vascular injuries and their complications (such as arteriovenous fistulas).

With the rapid and wide expansion of the scope of vascular surgery the demand for vascular replacements — grafts and prostheses — has grown apace. The pioneering work of Carrel on vascular transplantation[1], done at the turn of the century and its results long dormant, has been revived and extended by many workers. As a result of these efforts — the detailed review of which is not our present purpose — some important problems related to the replacement of vascular segments have been solved. While many unanswered questions still remain, the recent advances in our knowledge of vascular grafting have made it possible to turn into reality the idea of a *vascular bank*, the agency that assures a constant supply of arterial grafts. In what follows we shall attempt briefly to describe — for the most part on the basis of our own experiences at the Henry Ford Hospital — the organization of such a unit. We shall begin with a short review of the types of arterial substitutes that are at present at the disposal of the surgeon.

TYPES OF VASCULAR REPLACEMENT.

The type of vascular graft first used on a wide clinical scale, and still the most popular, is the *homologous arterial graft*.[2,13] Except for autogenous arterial graft—the use of which is, of course, a practical impossibility—this type of replacement most closely approaches the ideal substitute. It can be used in any situation: in the replacement of large or small, short or large segments.

Autogenous vein grafts serve well in some situations, but are subject to serious limitations of usefulness. They are unsuited for aortic replacement and they often fail in replacing long, narrow segments. They can be used with a good degree of success however to substitute for short and narrow arterial segments, in other words, in situations often created by traumatic injuries. *Homologous vein grafts* have the same advantages and shortcomings as autogenous vein grafts, but perhaps to a more pronounced degree.

Homologous arterial grafts have received a very extensive clinical trial (the number of cases in which they have been used must be well over a thousand) and have so far shown no serious inherent undesirable qualities; the rate of success with their use has been generally high, and the failures have been for the most part attributable to causes extrinsic to the grafts. Nevertheless the search for other types of arterial replacement

From the Departments of Surgery and Pathology.

is intensive, and for good reasons. First, the obtaining of arterial homografts is still a complicated task. It requires the cooperation of many people and the good will of the lay public. Until recently these grafts had to be gotten with aseptic precautions,—a truly formidable job. Secondly, certain misgivings are entertained by many concerning the fate of homografts after longer periods of observation then hitherto obtained. While it is now generally accepted that a homograft merely serves as a framework for the ingrowth of host tissue by which it is completely replaced,[14,20] there remains some serious concern that the fibrous tube that results may become calcified or undergo aneurysmal dilatation. It should be added, however, that observations of short aortic segments for over seven years, of long aortic segments (including bifurcations) for over three years, and of long, narrow segments for over two years have failed to reveal degenerative changes of importance.

To overcome the difficulties of procurement, *heterografts* have been tried both experimentally and, on a very small scale, clinically. In general grafts of this type fail in such a large number of instances as to make their clinical use impractical.

Another class of arterial substitutes promises to overcome both the scarcity and the doubtful future fate of homografts. These are the *prostheses made of plastic textiles*[24,27]. One can readily see the great potential value of the ease of storage and ready availability of such artificial vascular substitutes. It has been demonstrated by many that cloths woven of certain types of plastic filament (nylon, orlon, dacron, and others), when implanted, are accepted by the body with minimal tissue reaction. When such a cloth is shaped into a tube and the tube is inserted to replace arterial segments, it will not only be accepted by the surrounding tissues but a new arterial wall will be built on its framework. This new artery has a connective tissue wall and a psuedo-intimal lining that appear to be quite similar to those that, in time, replace a homograft. The organization of the new artery, however, laid down around the plastic prosthesis is generally more orderly, since there is much less foreign body reaction in the recipient tissues. This surprisingly effective arterial regeneration around the prosthesis has raised speculative hopes that the newly formed vascular channel will be less likely to undergo degenerative changes than a homograft would be. In clinical practice, in certain circumstances, during periods of observation up to two years, plastic cloth prostheses have been found entirely satisfactory. Good results have been noted in the replacement of a simple aortic bifurcation, or of a short and broad arterial segment that does not cross a joint. But even in replacing the aortic bifurcation, one must reckon with the disadvantage of having to tailor and sew the prosthesis, for, whereas seamless straight tubes of plastic textile are available, so far the technique of weaving a bifurcation has not been mastered. Aside from this shortcoming, plastic cloth prostheses have the defects of easy wrinkling when bent, and of complete lack of elasticity; mainly owing to the last-named property such protheses have been unsuited for the replacement of long and narrow arterial segments.

Plastic textile prostheses undoubedly have a brilliant future, for their present undesirable qualities will most likely be eliminated. At the present, however, homografts remain the most desirable arterial substitutes.

THE PREREQUISITES OF A SOLVENT ARTERY BANK

From the foregoing it is evident that the currency of the artery bank of the present day is the arterial homograft. To extend the metaphor, in order to keep the bank

solvent the following requirements must be met:

(1) There must be a supply of homografts sufficient to satisfy the demand.

(2) A method of storage must be available to allow the preservation of grafts for a relatively long period of time; without this prerequisite the loss through deterioration of such a perishable material as vascular grafts would make the maintenance of an adequate supply impossible.

Factors influencing the source of homografts. The adequacy of the source of homografts in a given hospital is determined by many factors such as the size of the institution, the criteria of acceptability of the grafts (in particular as regards the age and cause of death of the donor), the degree of cooperation of the hospital staff and, perhaps most importantly, the ease of procurement of the graft at the time of autopsy. With respect to the last-named factor, until recently the greatest single obstacle in the way of obtaining grafts was the aseptic technique of removing the arterial segments, requiring several hours and leading to delay and loss of time that inevitably alienated the pathologist; as will be seen presently this great impediment has now been done away with. These factors will now be considered singly.

As regards *the smallest general-hospital population* that can provide enough autopsy material to assure a satisfactory graft supply, extrapolating from the experiences at the Henry Ford Hospital, one can postulate that an artery bank is not practicable unless the hospital has 250 beds or more and the autopsy percentage is fifty percent or higher. The following factors enter into this calculation. In a typical general hospital there will be approximately one death per bed per year; in a hypothetical case of a hospital with 250 beds, this figure will, of course, be about 250 deaths. If the success of the hospital in obtaining autopsy permits is fifty percent there will be about 125 autopsies in course of the year. Of this number (on the basis of criteria to be discussed presently) about twenty percent or twenty-five cases will be potential donors of grafts. With a very well indoctrinated house staff, the necessary permits will be obtained for about twenty of these twenty-five potential donors. It would seem that twenty donors will supply sufficient graft material to justify the investment for a modest artery bank (which ranges from $1000 to $3000, depending on the type and scope of equipment) and to satisfy all the possible demand for graft material.

In our experience the criteria for the *qualities of acceptance of a usable graft* have changed greatly during the past two years. It has been found, for instance, that with the sterilization technique employed the cause of death has lost most of its importance as a contraindication to the use of a given graft. Satisfactory grafts have been obtained and inserted with complete success from patients who died of the following diseases: malignant hypertension, various forms of carcinoma, brain tumor, postoperative peritonitis, retroperitoneal sarcoma, Hodgkins' disease, purulent encephalitis and heart disease. It has been found, moreover, that usable grafts can often be obtained from patients over fifty years of age. In a survey of the experience of the Henry Ford Hospital artery bank during the past eighteen monthes among the thirty-seven donors from whom sixty grafts were obtained, the age varied from seventeen to sixty-one years with a mean age of 37.4 years. As a result, our instructions to the house staff state that permit for tissue removal should be obtained in all cases between the ages of twelve and sixty years. A member of the artery bank staff is present at every autopsy for which tissue permit has been signed, and inspects the arteries. The decisive factor in judging whether an artery is usable or not is the state of the physical qualities of the artery. When the

cadaver is properly refrigerated it is possible to obtain grafts without postmortem changes as late as twenty-two hours after death. The time that elapsed between death and autopsy in the cases that supplied grafts for the Henry Ford Hospital artery bank varied from one to twenty-two hours with a mean of 8.2 hours.

A factor that must be ranked very high in a plan for a functioning bank is the *co-operation of the house staff*. Since it is necessary to have a special permit for every arterial graft and since the permits are usually secured by the internes and residents, the truth of this statement is easy to see. The help from the house staff is readily forthcoming once the purpose and needs of the bank are understood. This requires repeated indoctrination. In reminding the house staff of their duty it is helpful to have the tissue removal permit attached in some form to the authorization for autopsy.

The crucial phase of graft procurement is the actual removal of the graft material. When this was done with aseptic technique the practical difficulties were almost insurmountable. As has already been briefly mentioned there are at present effective *methods for sterilizing arterial grafts* after their removal at routine autopsies without asepsis. High voltage irradiation (from a cyclotron or a cobalt bomb) has been used by some[28,30], and chemical sterilization with ethylene oxide[23], has received very extensive clinical trail. The results of irradiation have not been uniformly good; this method has the disadvantage, moreover, of lack of easy availability. Ethylene oxide, while apparently quite effective, is cumbersome to handle since it is volatile and explosive.

Beginning two years ago, and following the experimental work of Hartman and Lo-Grippo[31], and Trafas and his associates[32], we have developed a method of sterilization utilizing *betapropiolactone* in 1% (w/v) solution[33,34]. Before the method was put to clinical use, extensive experiments on human autopsy material proved that immersion of arterial segments in 1% betapropiolactone for two hours at 37°C did not appreciably alter the elasticity, tensile strength or histological structure. The procedure of sterilization now employed is as follows:

The arterial specimens are obtained in the autopsy room without aseptic precautions after the pathologist has removed all the thoracic and abdominal organs. The entire aorta is removed from the level of the ascending limb, down to the bifurcation and beyond, as far as technically feasible to dissect. Whenever the permit allows, through special incisions, the femoral arteries are also taken. It facilitates dissection and does not compromise the usefulness of the graft to transect the aorta at the level of the diaphragmatic hiatus. The vessels are removed by a member of the artery-bank staff because it is important to exercise caution in cutting the smaller arterial branches; these branches must be left with stumps of 2-3 mm. to make possible easy ligation just before use. It is of great importance to tie, by means of very heavy black silk left long, for identification by the undertaker the following branches: innominate, common carotid, subclavian, internal iliac, and external iliac arteries. It is most desirable to cannulate with long plastic tubes, for the embalmer, the deep femoral and popliteal arteries when the common and superfical femoral arteries are also taken.

The processing of the graft is carried out in three steps.

1. After its removal the graft is washed in sterile saline and the saline wash is cultured. The graft is now taken to the blood vessel laboratory where the periarterial fat and areolar connective tissue are carefully trimmed away. As formerly mentioned the stumps of the branches are not ligated until the time of use.

2. A familiarity with certain properties of betapropiolactone will be useful at this point. While quite stable in concentrated form, in watery solution at room temperature BPL rapidly hydrolyzes and loses its sterilizing effectiveness. Keeping low the temperature of the solutions, to be described presently, until the actual beginning of the sterilizing process reduces this hydrolysis. In hydrolysis, acid breakdown products are formed; hence the need for careful control of the pH throughout..

The clean vessel is next transferred to a container (preferably a wide-mouth glass jar 8 x 16 cm., with a screw cap) kept in ice, in which has been placed a quantity of buffered normal saline.* The volume of buffered saline used depends on the size of the artery to be sterilized. Specimens no larger than abdominal aorta with the common iliac arteries attached may be sterilized in a volume of fluid of 225 ml.; larger specimens require a volume of 450 ml. To the flask containing either 225 ml or 450 ml of buffered saline is now added 25 to 50 ml., respectively, of 10 percent BPL.** The addition of betapropiolactone solution is done slowly and under vigorous stirring, care being taken to bring the solution in contact with the entire inner surface of the jar and cap. The flask is now placed in a water bath for two hours at 37°C. From this time on the vessel must be handled aseptically.

3. At the end of two hours the graft is taken out of the flask under an ultraviolet hood, washed in a .2 molar phosphate buffer (7.4) and transferred to a storage flask. It is practical to use a Fenwal storage flask with a rubber stopper, which can be punctured with a needle to withdraw fluid for ascertaining sterility. The sterilized graft may be stored in any of a number of isotonic or nutrient solutions, or it can be lyophilized in precisely the same manner as a fresh graft.

Grafts prepared in this manner have been used in sixty grafting operations with an overall success that compares favorably with the results reported in the literature with grafts otherwise processed. These cases can be classified in the following manner (with the rate of early patency in parenthesis): Replacement of aortic bifurcation for aneurysm 17 cases (100%), replacement of aortic bifurcation for aorto-iliac occlusion 17 cases (100%), replacement of ileo-femoro-popliteal segments for occlusive disease 32 cases (82%), replacement of ileo-femoral segment for aneurysm 2 cases (100%), replacement of popliteal artery for traumatic contusion 2 cases (100%). Whereas cultures of the grafts obtained at autopsy showed growth of bacteria of a great variety, all the cultures obtained after sterilization were negative. No wound infection was observed.

Method of Storage.—The oldest method of storing homografts is that utilizing some nutrient fluid medium.[35] This method originated in the days when great importance was attached to the viability*** of the graft and every effort was exercised to assure the persistence of this quality until the time of use. Viability of grafts can actually be preserved for two to three weeks after the beginning of storage but it is now quite unanimously held that it is not a quality essential for successful clinical use. The

*The buffered saline solution is prepared by adding 1.68 gm. $NaHCO_3$ per 100 ml. of saline, or 4.2 gm. for 225 ml. and 8.4 gm. for 450 ml. of solution. For indicator phenol red is used (5 mg. per 100 ml. of saline.)

**To make 10% BPL solution, add 2.2 ml. of concentrated BPL (sp. gr. 1.140) to 25 ml. of ice-cold water. This solution must be made fresh and kept cold (on ice) until used. (Betapropiolactone can be purchased from the B. F. Goodrich Company, Brecksville, Ohio.)—A practical way to store BPL is to seal it in 2.2 ml. ampoules (enough to make 25 ml. of 10% solution) and keep the ampoules in the refrigerator.

***Viability is an elusive term. It is generally taken to mean the capacity of the graft to display growth in tissue culture.

great drawback of wet storage is its time limitation; while opinions vary as to the exact length of safe storage it is agreed that preservation in fluid medium for more than sixty days is unsafe; we believe that thirty days is the safe limit. Because of this time limitation wet storage is not suitable as the sole method of preservation for artery-bank practice.

Longer storage time without deterioration of the graft is possible with quick freezing at very low temperatures (—70°C) and placement in a deep freeze.[36,37] A graft can be safely stored in this manner for six to twelve months. The disadvantage of quick freezing is that once the graft is brought back to normal temperature it cannot be refrozen without sacrificing some important physical qualities. Other minor disadvantages are the difficulty of transporting the graft and the fact that the conditions of storage are often conducive to contamination.

The generally most satisfactory long-term storage method is freeze-drying (or lyophilization).[38-42] This method consists in quick-freezing the graft at temperatures around —70°C and in the dehydration of the graft under vacuum. The dehydrated graft is then stored in vacuum or in a nitrogen atmosphere. Storage can be maintained almost indefinitely but certainly as long as two years. The reconstitution of the graft is accomplished by placing it in saline for a period of from 30 to 45 minutes. If the graft is not used after being reconstituted, refreezing it again jeopardizes its physical qualities.

Freeze-drying kills the tissue cells and, therefore, in effect the process turns the arterial segment into a dead prosthesis. Very extensive studies have failed to show that this influences the rate of clinical successes adversely. Indeed it has been suggested, not very convincingly, that termination of the viability of the graft tissues is an advantage.[43] Perhaps the only serious disadvantage of the freeze-drying method is its cost, lyophilizing equipment ranging in cost from one to five thousand dollars.

In the artery bank of the Henry Ford Hospital a combined method of preservation has been in use. In spite of its disadvantages, wet storage offers some definite if minor advantages: it permits the quick use of the graft, without the waste of time required for reconstitution or thawing, and if the graft is not used, it allows resterilization or/and replacement in the storage solution without loss of the graft. In order to make use of these advantages, we store our sterilized arterial grafts in Hanks' solution[2] up to but not over thirty days. If the graft is not used by then, it is freeze-dried. In this manner the waste of graft due to wrong choice of segments is reduced to a very small figure.

SUMMARY

Without the expansion of the field of vascular surgery, the need for vascular grafts is becoming more widespread. With current methods of sterilization and preservation it is possible to establish a solvent blood vessel bank in most general hospitals with a hospital population over 250 and autopsy percentage of not less than fifty percent. Such a bank can assure an adequate supply of arterial homografts, the type of arterial substitute still the nearest to the ideal. The criteria of selection of grafts, a method of graft sterilization utilizing betapropiolactone, and the combined method of wet storage and lyophilization are described. The results in sixty grafting operations in terms of early patency utilizing arterial homografts processed in the manner described are summarized.

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PSYCHOTHERAPY

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The subject of psychotherapy has been talked about and written about so much in recent years that it would seem that there is nothing left to say. My excuse for adding to the discussion was a suggestion from your committee that this topic would be suitable for a place in this season's series of addresses before the Henry Ford Hospital Medical Society. The importance of psychotherapy has been so emphasized through all the media of communication as to convey the idea that it is virtually all there is to psychiatry, that it is a large part of general medicine as well, that is is even on the way to becoming a new religion that if applied in the right places could save our poor old sick world.

But there are other views too. There are medical men who wouldn't listen to a lecture on psychotherapy. An eminent surgeon whose scoffing attitude was known was asked how much psychotherapy was used in his own work. "Not a damn bit," he replied emphatically. Of course that wasn't true. He *was* using it, even if unwittingly. No good doctor can avoid using it. Another physician told me that if a patient came to him with a hypochondriacal "organ recital" requiring psychological treatment, the kind of psychotherapy he administered was such as to make the patient angry so that he wouldn't come back. Possibly the doctor applied, unintentionally, a remedial shock therapy. Who knows?

As an introduction to our subject I should like to call attention to an article by Bowman and Rose[1] This article will repay careful reading. It contains many things that I might say, but it is easier to quote; besides, quoting comfortably shifts responsibility when touching upon controversial matters.

Bowman and Rose[1] conclude that the answer to the question: Do our medical colleagues know what to expect from psychotherapy, is "No." They find, to begin with, that there is confusion as to a distinction between the terms psychotherapy and psychiatry, and that in everyday usage these terms are "almost synonymous." There is no less confusion as to the distinction between the terms psychiatry and psychoanalysis, with the consequent erroneous assumption on the part of the laity and even of medical colleagues that psychotherapy and psychoanalysis are also synonymous terms.

The confusion in the minds of many physicians about what psychotherapy is and what it can do, Bowman and Rose[1] courageously account for:

> "That many nonpsychiatric physicians are confused about the methods, goals, and effectiveness of psychotherapy is in large part a reflection of the muddled state of psychiatrists themselves about the nature and status of their specialty."

They document this statement by referring to *The Psychiatrist, His Training and Development.*[2] As an example of the confusion referred to, Bowman and Rose[1] comment on the repetitious use of the term psychodynamics, one of those new words that crop up in psychiatry from time to time to cover uncertainty of meaning or divergence of opinion. This word, as they put it, is "now virtually a shibboleth." Their statement referring to this part of the report is startling:

> "This is a valiant attempt to formulate a scientific basis—a psychodynamics—for our psychotherapy, but it appears to us to be only partially successful. It is not surprising that the wording of the report on psychodynamics is at times almost tortured, so great are the differences among the essentially irreconcilable

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opinions it must compose. A clear indication of the highly subjective nature of the opinions of the contributors to this discussion . . . is the statement which appears on page 19: 'In formulating psychodynamics, individuals tend to select their postulates with strong feelings of conviction, in accordance with private feelings of group allegiances rather than public knowledge.' We submit—if psychiatric scholars and practitioners of distinguished experience find it necessary to describe their methods of arriving at psychodynamic formulations as being mainly subjective, we ought not to be surprised at the bewilderment of our science-minded colleagues in the more concrete fields of medicine."

Ever since mental healing emerged from magic, charlatanry, or rank empirism, and struggled to become rational, if not yet quite scientific, it was recognized that the psychoneuroses were the conditions most amenable to psychotherapy—pithiatric disorders Babinski called them, i. e., brought on by suggestion and cured by the same means. And it was also a matter of common experience that the neuroses would yield to the greatest variety of treatment methods, whether applied by doctors, lay healers, and quacks, or through visits to sacred shrines.

In the paper by Bowman and Rose[1], from which I have quoted, these authors refer to the results of treatment of psychiatric disorders by different investigators and different methods with the finding that approximately the same range of favorable results followed "regardless of the methods used," and further that " the common denominator of improvement has nothing to do with the psychodynamic formulations and methods of specific psychotherapies studied, a point of view with which we readily concur." To the question whether one technique is better than another they give a forthright answer:

"In the studies which have been made thus far, comparing the effectiveness of different psychotherapeutic methods, no differences have been uncovered."

To account for the critical attitude in outside opinion toward psychiatry and in particular toward psychotherapy, and as a warning to those who would pin their faith on one or another special technique, Bowman and Rose give a final admonition:

"Most of the confusion among psychiatrists and nonpsychiatrists alike comes from our tendency to believe that psychotherapy is more exact and scientific than it is or can be."

After this jeremiad, for which—although I fully subscribe to their statements—Bowman and Rose must be held responsible, what can be said on the constructive side? We haven't yet got our definition. The *Psychiatric Dictionary* of Hinsie and Shatsky[3] defines psychotherapy as "the art of treating mental diseases;" turning to the word psychiatry, we find it defined as "the art of treating mental diseases." The second definition is better than the first, but the two terms are certainly not synonymous.

In simple language a definition might read: psychotherapy is the scientifically directed influence of the mind of the doctor on the mind of the patient in promoting health. This indicates, first, that it is a medical procedure; and second, the words 'scientifically directed' distinguish psychotherapy from faith-healing or other procedures in which the patient remains passive, bringing only his hope and awaiting the miracle. Of this more later.

A preliminary consideration is the part that psychotherapy should play specifically in psychiatric treatment, and also in medical treatment generally. From one point of view it would be correct to say that it is the important feature of all treatment,

in that it should accompany all treatment. But there has been a tendency in some quarters to carry this point of view to the extreme of making psychotherapy virtually the exclusive treatment of psychiatric disorders belonging to the so-called functional or emotional group. Overemphasis on psychotherapy involves the risk of missing fundamental organic or physiological conditions that require attention. Treatment takes its indications from etiology; and etiology is always multiform. Psychotherapy is therefore only a part, although a vital part, of what is called the Total Push. The term was coined by Myerson to bring out the fact that treatment in mental hospitals was more often than not only partial. The term total push should be unnecessary just as the expression psychosomatic medicine is unnecessary. All medicine should be psychosomatic and all treatment should be total.

In one of his lectures Huxley said that science is just trained and organized common sense. Medicine is a branch of science, and psychiatry is a branch of medicine, and psychotherapy is primarily a part of psychiatry. It is therefore essentially a medical procedure—at least it is in Michigan. Let us hope the example this state has set will be followed elsewhere.

But psychotherapy must also qualify as organized common sense. It should not be beyond the understanding of the literate layman. And the patient, if treatable at all, should be able to grasp it, or grasp at it, if only gradually—because treatment to be worth anything must be teamwork in which doctor and patient collaborate planwise. The patient is not passive and the doctor is not domineering—the one giving and the other receiving, or as one colleague facetiously remarked, the one doing and the other being done.

The doctor-patient relationship, if properly balanced and controlled (and ethically sound, it should not be necessary to add), is the crux of the matter. Therein lies the true quality of psychotherapy. The nature of the relationship is essentially educational—educational rather than instructional, having regard to the etymology of those two words. Education, drawing out, that is the important thing—obtaining the patient's spontaneous and full expression of his own point of view to which the doctor contributes no element through either suggestion or reading-in. The autognosis, to begin with, is more useful than a diagnosis.

Association tests may sometimes offer clues, but we have to remember that there is no such thing as "free association." For that we would have to create a situation entirely without either external or internal environment for the person being tested. The mind would have to function *in vacuo,* so to speak, like a disembodied spirit.

The conditions of the psychiatric interview should be the simplest, easiest, most natural possible. The couch interview is, I think, in every way objectionable. When two persons meet to discuss a problem one of them does not ordinarily lie down, although it may be understandable that sometimes the doctor might like to take the more restful position. In Joseph Wortis' entertaining little book recently published, *Fragments of an Analysis with Freud*[4], he described in detail the manner of the analytic hour as well as its content. The session proceeded in the orthodox fashion with Wortis on the couch and Freud sitting behind the head of the couch. He explained that he had adopted that arrangement because for one thing, as he put it, "I don't like to have people stare me in the face." A strange thing for a physician to say! Jung offered a more explicit reason for the doctor's position behind the patient. It gave him greater protection from the impact of the patients' transference.

Wortis kept full notes of each session and later on sent his manuscript for advice to Havelock Ellis with whom he had discussed his project before going to Vienna. Ellis commented that the report appeared to constitute an analysis of Freud rather than of Wortis and urged publication but not during Freud's lifetime.

Prerequisite for any psychotherapy is to find out what started the trouble. I am in agreement with those who seek first of all in the patient's present situation rather than in his remote past for the significant causal factors. This does not mean that we should neglect any period in the patient's history, the data of inheritance, or life experiences throughout. It does indicate the etiologic importance of current and recent happenings and conditions in his social environment, domestic, occupational and other. The role of repression has, I suspect, been considerably exaggerated. The pathology of memory must not be overlooked, but we may as well remember too that there is such a thing as healthy forgetting. Moreover it is useful to keep in mind the real danger of inducing too much introspection in the therapeutic process. The Socratic injunction, "Know Thyself," implies wholesome introspection. But individuals differ in their capacity to introspect normally, and in many patients introspection has already grown morbid and become a symptom of illness. To turn such a patient's thoughts inward in tracing the minutiae of his life history may be directly contra-indicated. An introspection neurosis may be engrafted on the already existing psychopathology.

And now a word about words. In discussing morbid mental states it should be possible to avoid esoteric language and keep within the framework of organized common sense. Likewise, we should not feel the need to resort to complicated or speculative interpretations when simple and more obvious ones will serve. We have an ancient term for this rule—Occam's Razor. This cutting instrument is quite useful in psychiatry, and especially in psychotherapy, an excellent pruning knife for verbal excess baggage. The statement of William of Occam which came to be known as the Razor was:

"It is vain to do with more what can be done with fewer."

The fine-spun elaborations of the psychotherapeutic process that sometimes appear in print in our time are curiously reminiscent, by some puckish association of ideas, of those marvellous mechanical contraptions in the Goldberg cartoons of a few years back.

We need more semantics in psychiatry, more semantics and fewer neologisms. We are still ridiculed for our professional argot. A new word should be coined only under two conditions: (1) when it denotes a new meaning, that is, one not already covered by a term in common use; (2) when that meaning can be clearly stated so as to be understood and accepted. Words that do not meet these conditions are bound to be used differently by different writers and so acquire an ambiguous or fuzzy quality. So many conflicting views were expressed in the Conference on Psychiatric Education[2] that the editorial committee gave up in despair. In their own words they simply "didn't try to reconcile the differences."

It is our common experience that each case is unique and cannot be fitted into any preconceived scheme. One may be permitted to suspect that the therapeutic couch may have Procrustean features. It is axiomatic that treatment must be individual and will vary from patient to patient. But what is true of the patient is also true of the doctor. The resourceful physician presumably will not attempt to follow unquestioningly any fixed school of teaching. Medical education does not standardize the personality of the doctor. Each will and should have his own manner of dealing with

patients, developing a flexible psychotherapeutic technique best suited to his own nature.

Sir William Osler was one of the most effective psychotherapists I have ever seen in action; and yet, during some 200 hours as a student under his teaching, I never heard him use the word psychotherapy, or offer any specific directions for applying it. He exemplified it in every contact with his patients.

The reverse of psychotherapy is the iatrogenic symptom, unfortunately not an uncommon reaction when the instructor accompanied by a group of students unguardedly discusses the patient's condition at the bedside. In one case, during the physical examination of an anxious patient the physician casually and unnecessarily remarked that the right breast was slightly smaller than the left. This started in her mind a new worry which grew at length into a fixed belief that the entire right side of her body was atrophied. By use of a tape measure she believed she found differences that supported her belief and eventuallly even experienced weakness in the right leg. In another case a neurotic youth with a functional heart condition was advised, without proper reassurance, to stay in bed for a few days. He developed panic, became obsessed with the idea of serious heart disease, and for many weeks could not be persuaded to leave his bed.

Fashions change in treatment as they do in dress. The history of psychotherapy as set forth in Bromberg's[5] recent book is an amazing record of these changes. We used to give bitter medicine for complaints called 'imaginary"—valerian for hysteria. Incidentally there are no imaginary complaints, as that term is commonly understood. If a person imagines he is sick, he *is* sick, but the sickness may be in the imagination itself and not in the place where he imagines it is. As a morbid mental state it therefore becomes a psychiatric problem.

Many years ago there was the vogue of the so-called water cure, still earlier the blue glass treatment, also various shock treatments, some of them almost incredibly crude, and electrical therapy was extensively used long before Cerletti and Bini[6] standardized it.

But we like to think the psychotherapy of today is rather more scientific than the crassly empirical methods of an earlier time. Our techniques, we trust, show a measure of organized common sense. This much I think we can say: the goal of psychotherapy is autotherapy. From the beginning, or early in the course of treatment, the patient is taking an active part in his own cure. He and the doctor are working together on a planned educational and training program. If all goes well, the patient gradually takes over more and more responsibility for the conduct of his own case. It is often possible to induce him to take constructive steps unawares. In such case the element of surprise and satisfaction when the fact of his self-directed effort is brought forcibly to his attention may lead him a good step forward. He is now answering his own questions and making his own decisions. An interesting device at this stage is to pose a hypothetical situation, not unfamiliar in his own experience, as if it were that of a friend seeking his advice. What would he offer? His reply may contain surprisingly sound therapy which can be turned to good use in his own progress in self-treatment.

In this collaboration effort the doctor tries to do what every good physician is supposed to do—make himself less necessary, eventually even unnecessary. The duration of training may be shorter or longer depending on many circumstances which will suggest themselves. No medical treatment should be extended beyond indubitable

need. There is danger that an unduly protracted therapeutic discipline may subdue the patient's mind to a morbid habit of introspection and dependence. By its very nature psychotherapy should be self-limiting. It ends as soon as the patient feels sufficiently assured and capable of taking charge of himself.

There is one point on which there could hardly be disagreement, namely, that psychotherapy is not solely the province of the specialist, i.e., the psychiatrist. Many psychiatric problems are brought first to the general physician, perhaps only to him. He should feel it his responsibility to deal with a large share of those problems. Indeed he, as the family physician, may be the most suitable person for this service. The term "general practice" surely means the whole medical field. It can not be "general" if psychiatry is left out. Alvarez in his book, *The Neuroses*,[7] has much of value to say on this subject.

If medical men interested themselves more widely in the psychological side of their practice the clamor for more and ever more psychiatrists would conceivably be less urgent. It would also be measurably less, we may hazard the guess, if it were not currently so fashionable to pay frequent visits to the psychiatrist, more specifically the psychoanalyst. This addiction seems to have reached considerable proportions, and the person is not altogether a rarity who would hardly make a major move without consulting his or her analyst, who, for the devotee, appears to have taken over more or less the function of priest.

There is a special feature of psychotherapy, for those who really need it, that merits thoughtful attention, and that is the educational value of invalidism. The patient's whole attitude may be changed if he can be led to realize that a period of illness is not quite time lost, indeed that it may prove to be a good investment in future mental well-being. Experience, we are told, is the best schoolmaster; illness is an experience; its lessons should be turned to account for the information not only of the physician but for the patient as well. If his trouble has been relieved and he had taken his full share in the restoration process, he has learned something about himself and about others that he probably did not know before; he has acquired some rudiments of psychology, normal and abnormal, and should be able to make a new assessment of his own resources. The doctor will take pains to point out these possibilities and their lessons. We know from experience that this knowledge brought home to the patient can have prophylactic value as problems or difficulties threaten in days ahead.

But if psychotherapy should not be too long drawn out, neither should talks about it, like this one. Occasionally writers or speakers close by quoting a poem—usually an anticlimax. I shall not take that risk, but would like to cite one noteworthy instance of poetry reading by the patient as psychotherapy. It is from the autobiography of John Stuart Mill[8]. In the autumn of 1828 when Mill was twenty-two he found himself heavily overworked and became deeply depressed, desperately so. By some fortunate association of ideas, he was led to take up a volume of Wordsworth's poems. This step was possibly a reaction to the attitude of his father whose driving discipline was severe and austere and who, like Plato, held poetry in low esteem. In his autobiography Mill tells us that he had "no expectation of mental relief" from reading Wordsworth, but to his surprise it brought healing. "What made Wordsworth's poems a medicine for my state of mind was that they expressed, not mere outward beauty, but states of feeling, and of thought coloured by feeling, under the excitement of beauty. They seemed to be the very culture of the feelings which I was in quest of . . . And I felt myself

at once better and happier as I came under their influence. There have certainly been . . . greater poets than Wordsworth; but poetry of deeper and loftier feeling could not have done for me at that time what his did. I needed to be made to feel there was real permanent happiness in tranquil contemplation. Wordsworth taught me this, not only without turning away from, but with a greatly increased interest in the common feelings and common destiny of human beings."

Feeling, emotions, these are conspicuous words in current psychiatric literature. We even have a new and popular euphemism for mental illness—"emotional disorder." At any rate disturbed emotions play a central role in psychiatric conditions. In the quotation from John Stuart Mill's autobiography, the keynote, is the line, "the very culture of the feelings"—their training, not their indulgence; their control and direction, not giving them loose rein; the effort at least to modify or inhibit their expression—*the very culture of the feelings* is a major goal of therapy. Mill found that Wordsworth's poems can promote this culture and thus contribute to the healing process for a receptive mind.

For a final true word we turn to the *Anatomy of Melancholy:*

> "An empirick oftentimes, and a silly chirugeon, doth more strange cures than a rational physician . . . because the patient puts his confidence in him, which Avicenna prefers before art, precepts, and all remedies whatsoever . . . He doth the best cures, according to Hippocrates, in whom most trust."

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MEDICAL STAFF CONFERENCE

J. G. MATEER, M.D., PHYSICIAN-IN-CHIEF, *Presiding*

SUBJECT: PSITTACOSIS

CHAIRMAN: E. L. Quinn, M.D.*

PANEL: D. C. Bunch, M.D.**

W. R. Eyler, M.D.*** G. Vetne, M.D., Medical Resident

W. C. Montgomery, M.D., Intern J. Lovett, M.D., Medical Resident

R. S. McGraw, M.D., Intern

Dr. Mateer: This conference will deal with the diagnosis, therapy, epidemiology and pathogenesis of psittacosis.

Dr. Quinn: We shall develop three aspects of psittacosis: First, to define the diagnostic features which will make the disease recognizable to the clinician; second to examine critically the experimental and clinically used therapeutic agents in psittacosis; and thirdly, to review the position of the psittacosis agent morphologically and immunologically among the virus agents.

CASE PRESENTATIONS

Dr. McGraw: Case No. 1. Mrs. I. M., H.F.H. No. 233836, is a 52 year old, white female who presented herself at the emergency room on November 21, 1954, with a chief complaint of chills, fever, and headache for one week and of feeling sick all over.

Her past history and system review were not contributory to the present illness.

The present illness began approximately one week prior to admission, at which time she noted the onset of severe headache, general malaise, fever and a mild sore throat. She worked for one day with these complaints, but then stayed in bed until seen at the hospital. The fever, chills, severe headache and malaise, along with anorexia, persisted all week without improvement. There was no cough, chest pain, epistaxis, vomiting, jaundice, dark urine or abdominal pain. The patient said she owned parakeets, one of which had died about one month ago.

The physical examination on admission revealed an acutely ill-appearing woman with a temperature of 103.4° F., respirations 28 per minute and pulse 95 per minute. The respirations were not grunting. The nostrils did not flare. The skin was hot and moist. The only other obnormal findings were limited to the chest. Slight dullness to percussion and a few rales were noted over the right mid-anterior chest.

The pertinent laboratory data was as follows: normal urinalysis; white blood count 9,600 per cubic millimeter with a normal differential; negative routine blood culture; negative cold agglutinin titer; unremarkable throat culture; sedimentation rate of 31 millimeter per hour (Winthrop). The complement-fixation test for psittacosis is revealed in Table I.

The hospital course of the patient was benign. She was placed on tetracycline (achromycin), 250 mg. four times daily, 12 hours after admission, and her temperature became and remained normal in 24 hours. Symptomatic improvement was rapid. The physical findings in the chest were normal by the 5th day. The patient was dis-

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This is an edited report of a staff conference of the Department of Medicine of the Henry Ford Hospital.

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charged on the 11th hospital day. She received a total of 9 grams of tetracycline.

Three weeks after discharge, she complained only of tiring easily and of the slowness with which her previous strength was returning.

Dr. Montgomery: Case No. 2. Mrs. B. B., H.F.H. No. 514105, is a 40 year old, white housewife who was admitted to Henry Ford Hospital on December 7, 1954, with chief complaint of headache and malaise of five days duration.

The family history was significant in that her sister (Case 1) had been treated at the Henry Ford Hospital in November, 1954 for psittacosis. This patient had been repeatedly exposed both to the sister and her sister's sick parakeet.

The present illness began five days prior to admission, at which time she developed severe occipital headache and general malaise. Three days prior to admission she noticed chills, fever, night sweats, dry non-productive cough, and a few episodes of mild epistaxis. These symptoms persisted until the time of admission. There were no gastrointestinal complaints or chest pains.

The physical examination revealed a normal temperature and respiratory rate. The pulse was 80 per minute. There was no jaundice, rash or lymphadenopathy. Examination of the lungs revealed only a few inspiratory fine rales at the right posterior base.

The laboratory data was as follows: The white blood count was 11,500 per cubic mm. with a normal differential; the sedimentation rate was 40 mm. per hour (Winthrop); urinalysis, negative; routine blood culture, negative; cephalin-cholesterol test, negative; cold agglutinin titer, 1:4. The complement fixation for psittacosis is revealed in Table I.

The patient's symptoms were unchanged until she was placed on tetracycline, 250 mg. four times daily, on the 5th hospital day and gradually subsided in the next five to six days. She received a total of 11 grams of tetracycline.

TABLE NO. I

PSITTACOSIS COMPLEMENT-FIXATION TESTS

(Performed by Dr. E. M. Yagle)

Case No. 1.	11/24/54	1:32	Case No. 2.	12/8/54	1:32
	12/1/54	1:28		12/14/54	1:64+
	12/17/54	1:64			

Dr. Eyler: Case No. 1. (Fig. 1.) There are multiple patches of consolidation with the largest patch at the right base. The consolidation is not very dense, and is interspersed with areas of aerated lung. In the right upper lobe just beneath the clavicle, overlying the first interspace and second rib, there is an additional area with aerated lung in the center, which suggests the possibility of cavitation. No well defined cavity wall is recognized. On the left side there are multiple strands radiating into the upper lobe. A differential diagnosis would lie between multiple foci of acute infection and chronic infection, such as tuberculosis.

(Fig. 2.) Two days later, only a few strands remain on the left and most of the process has cleared on the right side. There are still, however, strands of density in both of the areas previously involved.

(Fig. 3) By November 29, 1954, the process had cleared.

SUMMARY Initially, the pattern of densities and distribution raises the question of chronic infection, such as tuberculosis, as well as being compatible with a patchy pneumonitis of an acute type. The course establishes it as an acute infection.

The second patient, by comparison with the first, had very minimal changes with faint, diffuse consolidation in the right lower lung field. The films suggest that it is in

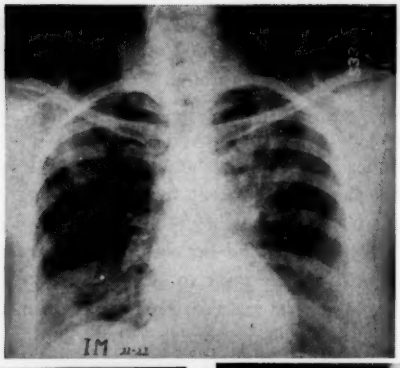

Fig. 1.
Case No. 1—
Nov. 21, 1954

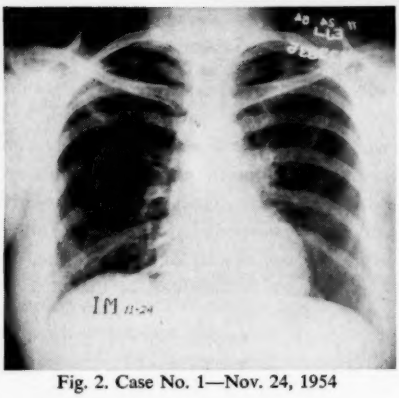

Fig. 2. Case No. 1—Nov. 24, 1954

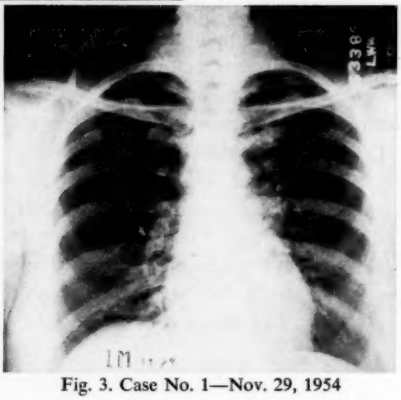

Fig. 3. Case No. 1—Nov. 29, 1954

the right middle lobe. There are old scars at the left base.

A progress film at four days shows only a few linear strands of atelectasis remaining in the area of previous consolidation.

SUMMARY This, too, is compatible with an acute pneumonitis which has cleared almost completely in four days. The consolidation was relatively diffuse.

Dr. Bunch: Historically, the family epidemic type of psittacosis was recognized long before the etiologic agent was identified. It is to be noted that the two patients presented this morning are sisters, that the sister who owns the parakeet was apparently the first one infected and her sister and brother-in-law both developed symptoms later. We have not had an opportunity to perform a complement fixation on Mrs. M's. brother-in-law. Interestingly enough, Mrs. M. states that her family dog became ill during this period of time also. As we shall see later, dogs are not usually included as hosts for this disease, but there was one family epidemic that was possibly initiated by the purchase of a sick dog from a bird shop where psittacosis was known to exist.

The onset of psittacosis may be either sudden, or gradual and insidious. It is probably more often sudden with chilly sensations, fever, marked malaise, anorexia, and perhaps even sore throat. The temperature usually ranges from 100. to 102. degrees F. at the onset and gradually rises. It may be present from seven to fourteen days. Cough is almost always present. Epistaxis occurs in one-fourth of the cases, a rare finding in primary atypical pneumonia. Nausea and vomiting are common. Diarrhea or constipation may be present.

One major characteristic of this illness is the discrepancy between x-ray findings and chest symptoms and physical findings. There may be a slight, dry, irritating cough, which in later stages may become mucoid or even mucopurulent, but physical findings in the chest may be limited to a few fine rales or slight dullness in spite of very marked x-ray changes. The x-ray presents patchy areas of pneumonitis which may range from very slight increased densities to marked involvement of both lungs. In the first patient presented this morning, the findings were so extensive that the immediate roentgenologic diagnosis on the first film was moderately advanced tuberculosis with probable cavitation. Ordinarily there is slow resolution on x-ray examination, although physical signs may disappear by the third week. Our first case was characterized by rapid resolution of her extensive lesions.

Ordinarily there is a bradycardia, but severely ill patients may present collapse, tachycardia and tachypnea. The size of the spleen is a controversial issue, some clinicians having reported its enlargement as a characteristic finding of psittacosis, yet the current literature implies that the spleen is palpable in only very few cases. "Rose spot" rashes have been noted, but are usually not part of the picture. Mental symptoms may occur especially in more severely ill patients and include disorientation, mental depression and delirium.

There is usually an absence of a leukocytosis. A definite leukopenia is present in only 25 per cent of the patients.

As regards complications, thrombophlebitis may occur and has been responsible for some deaths. Relapse is quite common and prevention of relapse requires most conservative management during convalesence.

Perhaps the most interesting pathologic characteristic is that the lungs may appear to be completely consolidated and yet microscopic examination shows that these areas are unevenly involved, and alveoli containing air or serum are dispersed throughout the consolidated portions. The liver may exhibit focal necrosis. The spleen may be enlarged and contain relatively small follicles and engorged sinuses filled with microcytic cells. Frequently, involvement of the kidneys occurs. Hemorrhages and capillary thrombi in the adrenals have been reported.

The complement-fixation test hsa become the most useful laboratory tool in confirming a clinical diagnosis of psittacosis. It is a fairly simple test to do, and the commercial antigen is quite reliable. Interestingly, there is a cross reaction between lymphogranuloma, psittacosis, and some of the other mammalian members of this group so that it is impossible to tell on the basis of the complement fixation test which one of the organisms is affecting the patient. Complement fixation titer begins to rise about ten days after the onset of the illness, but may take as long as 30 days to reach significant titers. Titers up to 1:64 have been reported during the first month of the illness; these are considered to be significant titers. They may actually go much higher than this. There are instances in which an anamnestic type of reaction has been reported producing a positive complement fixation test to psittacosis. It has been noted that if the illness were truly psittacosis, the complement fixation titer remained elevated for a year or more after the acute illness; whereas if it were due to another member of the lymphogranuloma-psittacosis group, of if it were an anamestic reaction, the complement-fixation titer would fall to low levels after about three months. Continued high level of a positive complement fixation titer to psittacosis after one year implies either continuous exposure, which might be experienced by

bird shop owners, or else a carrier state or chronic recurrent infections, such as reported by Meyer and Eddie[10].

In research laboratories, certain organisms of the lymphogranuloma-psittacosis group may be differentiated with neutralization test even though the complement fixation titer to both psittacosis antigen and "lygranum" may be elevated.

The organisms may be identified in biopsy or autopsy material. However, clinically this does not appear to be a practical mode of diagnosing the illness. The isolation of the agent from sputum is possible but not practical because of its extreme hazard to laboratory personnel.

Dr. Quinn: In summary one should think of psittacosis in patients who have symptoms of influenza, of viral pneumonia or of typhoid fever. One should then inquire as to symptoms common in psittacosis, but unusual in other respiratory viral illness, namely, epistaxis, nausea, vomiting, constipation or diarrhea. Next, we should inquire into the possibility of bird contact, including parrots and parakeets, and especially if the bird was recently ill. Another common feature is frequency of family occurrence, particularly in the winter months. Finally, normal routine laboratory findings including negative cold agglutination test, and chest x-ray findings of interstitial pneumonitis should lead the clinician to request paired blood specimens for complement fixation test with the psittacosis antigen. A positive titer of 1:16 or higher is quite suggestive in a single specimen. A three-fold to four-fold titer in paired acute and convalescent specimens is diagnostic of infection by a member of this group of agents.

Let us now examine the available reports and our experience in the treatment of psittacosis.

Dr. Vetne: The effect of penicillin treatment in psittacosis infection has been studied in animal experiments, mainly on mice, and in small series or in scattered cases on humans. It must be kept in mind that psittacosis in humans can vary from a very mild to a very severe infection. It is, therefore, difficult to evaluate the effect of penicillin in the relatively few human cases so far reported.

Eighty mice were inoculated with psittacosis virus by Heilman and Herell[1]. Forty of these had no treatment and showed 88 per cent mortality. In the forty other mice, penicillin treatment was started one to 17 hours after inoculation of psittacosis virus. Treatment was continued for seven days. In this group, there was only five per cent mortality. In another study on 104 mice, there was an eight per cent mortality in the treated group and 100 per cent in the untreated group. In both of these studies, penicillin-treated mice who recovered were sacrified thirty days later and examined for psittacosis virus. Liver and spleen in most of these animals were found to have inclusion bodies of psittacosis.

Meyer reports three human infections with psittacosis virus, successfully treated with penicillin. Treatment was started on the sixth to eighth day of illness and continued for eight to ten days after the patient had become afebrile, which usually occurred within 48 to 72 hours. Meyer points out the importance of continuing pencillin treatment for a sufficiently long period after the patient become afebrile. Relapse has been reported in cases treated with penicillin for only two or three days after the patient became afebrile.

Wolins[4] reports six patients treated with penicillin of which four recovered promptly with 400,000 units of penicillin daily. Two cases showed no response to penicillin for four or five days and finally they recovered "spontaneously."

Dr. Lovett: Since chlortetracycline (aureomycin) became available, there have not been sufficient cases of psittacosis available to provide for an extensive clinical trial. However, the results reported so far are very encouraging. In 1948 Wong and Cox[5] at a symposium of the New York Academy of Science, reported that chlortetracycline had an excellent therapeutic effect on experimental psittacosis infection in chick embryos and albino mice. Their work showed that the prolongation of life following the inoculation of chick embryos with psittacosis was directly affected by the size of the protecting dose of chlortetracycline, but that the protective action of the drug was not affected by the size of the inoculating dose of virus. In 1950, Gogolak[6] using chick embryos, showed that chlortetracycline prevented division of the elementary bodies of the virus and significantly inhibited their growth in size.

During 1949 and 1950, Henry Brainerd[7], Theodore Woodward[8] and Thomas Green[9] separately reported in detail on a total of six cases of psittacosis infection in humans treated with chlortetracycline. Two of these cases had previously failed to respond to treatment with penicillin. The dosages used varied from three to four grams in divided doses daily for a period of seven to ten days. The response to therapy in each of these cases was good and was indicated by a prompt drop in the temperature and by subjective and clinical improvements. The lung lesions as shown by X-ray were found to clear rapidly.

Karl Meyer[10], reports two deaths in a review of ninety-two cases in man, treated with chlortetracycline prior to 1951, a mortality of 2.5 per cent.

This mortality rate indicates improvement over the previously reported mortality rates of 18 per cent in approximately 600 cases during the 1929-30 psittacosis epidemic, 11 per cent for the cases reported between 1930-1940, and 9.3 per cent of 288 cases treated with penicillin between 1940-46.

In summary, chlortetracycline appears to be the drug of choice in the treatment of psittacosis infection at the present time. It prevents elementary body division and retards growth of the virus. One may expect drop in the patient's fever, and subjective and clinical improvement within 48 to 72 hours after beginning therapy, some clearing of the pneumonitis within four to seven days, may also be expected.

Dr. Quinn: We have treated five cases of psittacosis, three with penicillin and two with tetracycline. All responded favorably, but one of the patients treated with penicillin suffered two relapses. We noted repeatedly from the histories of our patients prior to admission, that short courses of either of these drugs was followed by relapse. Our feeling is that tetracycline is the drug of choice, but more important is the necessity of adequate therapy.

Dr. Bunch, will you review the pertinent points in the epidemiology and pathogenesis of this disease which are important in establishing the clinical feature of relapse and the need for adequate therapy.

Dr. Bunch: This psittacosis organism is characterized by predilection for psittacine birds. A number of other animals and birds have been reported as having had the disease or have been experimentally infected. These include many strains of mice, rabbits, hamsters, squirrels, monkeys, sparrows, domestic fowl and turkeys, doves and pigeons. Of course, man also may be infected.

The most common mode of transmission is probably by droplet infection. Humans have been infected from merely being in a room for as little as five minutes where an autopsy was being performed. Man to man transmission has been reported and is particularly dangerous for nurses and physicians in attendance of psittacosis patient.

The causitive organism is a particularly interesting organism. It is classified in the lymphogranuloma-psittacosis group of viruses. These organisms range in size from 250 millimicrons to 350 millimicrons, thus placing them between the true large viruses such as smallpox, and the rickettsia. Consequently, they can be seen with a light microscope with appropriate stains. Further, because of the ease with which they are seen, their life cycle has been studied.

These organisms may go through their life cycle either in an intracellular or extracellular phase. One or more virus particles may enter a cell. A common matrix is formed about a single virus particle. This single virus particle is known as an *elementary body*. About 24 hours is required for a particle to enter and form its matrix. After this time, the virus particle within the matrix begins to multiply and as multiplication progresses, particle size dcreases as the virus colony enlarges. The particles are always surrounded by common matrix and this plaque of numerous virus particles with its matrix is called an *inclusion body*. During the second 24 hour period, it may fill the entire cytoplasm of the cell. If the cell is doubly or triply infected, the other inclusion may parallel the initial one. After about 48 hours, the matrix of the inclusion body begins to liquefy and during the third twenty-four hour period, death of the whole cell occurs and rupture follows with the release of elementary bodies which are then infective for other cells. The extra cellular multiplication of these organisms follows a similar pattern.

The effects of penicillin and chlortetracycline on the life cycle of the organism has been studied. Penicillin apparently prevents division of the virus particle intracellularly, but there continues an abnormal growth of an irregularly shaped vacuolated plaque which maintains the ability to enter the host cell. With chlortetracycline, the virus particle division is prevented and the virus growth is suppressed to the point that even if small plaques did develop intracellularly, they have little or no effect on the invaded host cell.

There has been insufficient experience with tetracyclines clinically to be certain of any definite answers about their superiority. Regardless of whether penicillin or tetracycline is used, however, there is evidence that there continues to be intracelluar organisms for as long as one year after treatment. In fact, one case has been reported by Meyer and Eddie[10], of a patient who had developed a carrier state from which organisms were isolated as long as eight years after the initial infection. It is this tenacious persistance of the organism which predisposes to the clinical relapse which is common.

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ABSTRACTS OF RECENT PUBLICATIONS OF THE PROFESSIONAL STAFF OF THE HENRY FORD HOSPITAL AND THE EDSEL B. FORD INSTITUTE FOR MEDICAL RESEARCH

*GROWTH AND COENZYME. PAUL D. BARTLETT, PAMELA GRIMMETT, LOIS BEERS AND SHIRLEY SHELATA. Fed .Proc. 14:177, 1955.

Production of acute pantothenic acid deficiency in adult rats stimulated with growth hormone (Proc. Soc Exptl. Biol. & Med. 73:85, 1950), failure of pantothenic acid deficient rats to respond to growth hormone (Endocrinology 55:40, 1954), and the fact that metabolically active pantothenic acid appears to be largely bound in coenzyme A (J. Biol. Chem. 177:97, 1949) have prompted us to determine the coenzyme A content in tissues obtained from rats in different stages of the growth process. Expressed respectively in terms of Kaplan and Lipmann units of coenzyme A per gram wet weight, per 100 gm body weight, per 100 mg. homogenate total nitrogen, and per 100 mg. dry weight, the following concentrations of coenzyme A were found in liver tissue obtained from rapidly growing immature normal rats (group I)—150, 559, 450, and 50; from immature rats in which growth had been arrested by hypophysectomy (group II)—127, 406, 364, and 45; from hypophysectomized rats stimulated with growth hormone (group III)—119, 386, 340, and 40; from adult normal rats (group IV)—106, 284, 328, and 34; and from adult normal rats stimulated with growth hormone (group V)—122, 347, 373, and 42. Liver coenzyme content of group I rats expressed as units per 100 gm. body weight was found to be significantly higher than that of groups II, III, and IV rats, and that of group V rats significantly higher than that of group IV animals. Differences between groups II and III were not significant.

*METABOLISM OF METHYL—C^{14}-3-PYRIDYL KETONE *IN VIVO*. W. T. BEHER, MILTON MADOFF, G. D. BAKER, AND O. H. GAEBLER. Fed. Proc. 14:180, 1955.

Methyl-C^{14}-3-Pyridyl ketone (3-acetylpyridine) was synthesized and administered by intraperitoneal injection to a series of rats. At intervals samples of expired carbon dioxide, urine, and various tissues were obtained and assayed for C^{14} activity. The results showed that about 15% of the injected C^{14} appeared as expired carbon dioxide in the first seven hours. About 35% of the activity was recovered in the urine in 72 hours. The C^{14} content of the heart, brain, lung, and spleen was nil or very low at each time interval over a 24 hour period. Liver and kidney showed large amounts of activity which diminished with time indicating that these organs concentrate and metabolize methyl-C^{14}-pyridyl ketone. It was observed that kidney concentrated this substance to a greater degree than any other tissue in the first 6 hours after injection. However the greatest rate of excretion of C^{14} activity in urine occured in the second 24 hour interval. It is probable that methyl-C^{14}-3- pyridyl ketone is first concentrated in the kidney for metabolism rather than excretion inasmuch as kidney has been shown to metabolize this substance *in vitro*. Small intestine showed a sizeable activity up to 24 hours, probably indicating that the feces is an important route of excretion.

MECHANISM OF REDUCED CAPILLARY RESISTANCE PRODUCED BY MACROMOLECULAR INFUSIONS. V. G. BEHRMANN AND F. W. HARTMAN. Fed. Proc. 14:11, 1955.

Infusions (40 cc/kg. injected at 4 cc/kg./min.) of plasma expanders in intact dogs alter capillary resistance to a variable degree. Gelatin (5-6%) infusions are followed by prompt prothrombin and platelet recovery coincident with normal capillary fragility and negative autopsy findings. After Modified Fluid Gelatine, slow prothrom-

*From Edsel B. Ford Institute for Medical Research

bin and platelet restoration with only transistory bleeding tendency is seen. Intravenous dextran and PVP lead to deceased capillary resistance associated with thrombocytopenia and hypoprothrombinemia, similar to that previously described due to certain polysaccharide sulphate infusions which lead to thrombocytopenia, agglutination of platelets and reticuloendothelial deposition with hemorrhagic sequelae. Our observations of liver, spleen, lymph nodes and bone marrow support this concept, especially in dextran and PVP-infused animals. Data on intact and splenectomized dogs, infused with these macromolecular solutions on successive days, indicate that the spleen plays a role in the thrombocytopenia observed with dextran and PVP. Gelatin injections produced a similar response in both intact and splenectomized animals. In contrast to intact dogs, dextran or PVP infused splenectomized dogs showed partial platelet recovery and diminished bleeding tendency. In splenectomized dogs, platelet levels were higher 24 hours after gelatin (100-130% of initial level) than after dextran (60-80%), suggesting depression of platelet formation and/or removal by the remaining RES. Bone marrow was studied to investigate the former hypothesis and India ink-RES blockade in splenectomized dogs, prior to macromolecular infusion, was established to test the latter. Further confirmation was sought through observations on high molecular colloidal infusions, especially those formerly used as blood substitutes.

REGENERATION OF THE URINARY BLADDER IN THE DOG, FOLLOWING TOTAL CYSTECTOMY. A. W. Bohne, and P. J. Hettle. Surg., Gynec. & Obst. 100:259, 1955.

A series of dogs was subjected to total cystectomy, a plastic mold being inserted in the remaining extraperitonal space. The ureters were splinted with polyethylene catheters. At a second operation the catheters and the mold were removed, primary suturing of the "bladder" which had regenerated being accomplished. Microscopically it was found that this "bladder" became lined with transitional epithelium at 6 to 10 weeks. Functionally, a number of the animals voided in a normal manner. It is thought that a similar procedure is feasible in patients who need a total cystectomy, rather than the far from satisfactory ureterointestinal transplant or skin uretorostomy.

*VITAL STAINING WITH TWO DIS-AZO TEXTILE DYES. Robert H. Foulkes and William T. Beher. Stain Technol. 30:37, 1955.

Subcutaneous injections of 0.25% saline solutions of two dis-azo textile dyes, calcodur pink 2BL, C. I. 353, also known as benzo fast pink 2BL and amidine fast rose 2BL, and a blue dye, dianil blue G, C. I. 508, were made on alternate days on albino rats for one week. The blue dye is closely similar to Niagara blue 4B, C. I. 520, and dianil blue R, C. I. 465. Staining reactions were much like those of other vital blue disazo dyes. Although the pink dye exhibited a similar staining pattern, there were notable differences. The tissues of most glands were stained pink or red. Nuclei of the tubular epithelial cells of the kidney contained red granules as did the cytoplasm of the Kupfer cells. Most unusual was the bright red staining of the elastica interna of medium and large sized arteries.

*INFRARED AND X-RAY DIFFRACTION STUDIES OF DIGITONIN. Oliver H. Gaebler, Jonathan Parsons, and W. T. Beher. Anal Chem. 27:441, 1955.

Until recently, it has been difficult to secure digitonin that was uniformly satisfactory for determination of cholesterol. The present study was undertaken to determine whether lots of digitonin secured from various sources differ with respect to their infrared absorption and X-ray diffraction patterns, and whether these criteria

*From Edsel B. Ford Institute for Medical Research

might serve as a basis for recognition of satisfactory lots. Eight digitonin preparations from four different firms proved to be equally useful, although their X-ray diffraction and infrared absorption patterns differed considerably. This remained true whether the color reaction employed for estimating the digitonide was the Liebermann-Burchard reaction for cholesterol or the reaction which digitonin gives with anthrone.

*I. EXPERIMENTAL VERIFICATION OF THE MIE THEORY OF LIGHT SCATTERING. WILFRED HELLER, JOSEPH N. EPEL, RICHARD M. TABIBIAN, AND JOHN H. L. WATSON. J. Chem. Physics 22:1777, 1954.

Several thorough investigations published during the past 45 years left little doubt that the Mie theory of light scattering is in essential agreement with the facts. There has been no rigorous, quantitative proof which presupposes (a) the use of a system with spherical particles as uniform in size as possible, (b) an exact knowledge of their density and refractive index, (c) an optical precision instrument, and (d) a fairly reliable independent method of comparative size determination. In the present work poliptyrene and polyvinyl toluene lattices of very low heterodispersion were used and densities and refractive indices were accurately determined for them. A precision apparatus was used to measure specific turbidity by transmission and electron microscopy was used as an independent comparative second method. The agreement between optical and electron optical diameters was excellent and it can be stated that the Mie theory is in quantitative agreement with the facts. (see p1778 J. Chem. Phys., Vol. 22)

TISSUE DISTRIBUTION AND FATE OF HYDRACRYLIC ACID. A. R. KELLY, JAMES J. TAZUMA AND F. W. HARTMAN. Fed Proc. 14:409, 1955.

Previous publications (1951-54) from this laboratory have dealt with the use of B-Propiolactone (BPL) as a viricide for sterilizing plasma, biologicals and arterial homografts. These reports stress the low toxicity of the residual end-products of BPL hydrolysis. This paper deals with the biological distribution and excretion of hydracrylic acid (HA), the major *in vivo* and *in vitro* degradation product. Plasma and urine drug concentrations were determined in the dog, mouse and man at intervals following I. V. HA. Blood, urine and tissue HA distribution were studied in normal mice and compared with those following nephrectomy for production of experimental liver damage. HA concentrations were estimated by colorimetric analysis and paper chromatography.

In the dog plasma HA levels decline rapidly after injection, 40% of the total dose disappearing during the initial 30 minutes. All slope changes in the plasma time-concentration curve are reflected inversely in the excretion curve. Renal plasma clearances by constant infusion techniques are approximately equal to glomerular filtration rates at urine outputs above 1.5 cc./min.

The excretion rate is more rapid in the mouse, urinary HA accounting for approximately 65% of the total dosage. The liver has been implicated in the metabolism in this species. HA can be detected in all tissues and body fluids. Kidney: blood concentration ratios above 1.0 occur throughout the excretory period. Immediately after administration, approximately 86% of the total dosage can be recovered in the blood, kidney, liver, skeletal muscle, spleen and brain (tissues representing 55% of the body weight of the mouse). Skeletal muscle contains 47% of the dose at this time.

FUNCTIONAL SIGNIFICANCE OF SPINAL CORD LESION LEVEL. CHARLES LONG II, AND EDITH BUCHWALD LAWTON. Arch. Phys. M. 36:249, 1955.

The correlation between spinal cord lesion level and functional capacity is dis-

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cussed. In the absence of medical and psychiatric complications, the most important factor in this relationship is the distribution of the remaining muscle power. Early in the course of rehabilitation, functional goals can be outlined in general on the basis of the remaining muscle power. However, the great individual differences cannot be overlooked. Spasm, urinary infection, lack of co-ordination and lack of motivation are some of the most common restricting factors which may occur. A patient with any one or more of these complications may reach a more limited goal than another patient with less muscle power and no complications. Thorough training and constant practice in functional activities are essential for all patients. The patient with a cervical lesion has partial strength in his upper extremities. The patient with a high thoracic lesion has full upper extremity strength and is independent in transfer to and from the wheelchair, and in self-care activities. The patient with a mid-thoracic lesion has good upper extremities and thoracic stablization. The patient with a very low thoracic lesion has good upper extremities, thoracic and abdominal strength. The patient with a low lumbar or sacral lesion has full upper extremity and trunk strength, hip flexors and knee extensors.

CONSERVATIVE MANAGEMENT OF DIABETIC FOOT COMPLICATIONS. W. L. Lowrie, W. Earl Redfern, and Brock E. Brush. Postgrad. Med. 17:45, 1955.

This reprint is a reproduction of the Exhibit which received a Certificate of Merit at the American Medical Association San Francisco Meeting, June 1954. All colored photographs are reproduced in black and white. Included are summaries of the discussion of foot hygiene and the management of complications which appeared in this Bulletin 2:79, 1954.

CARCINOMA AND THYROID NODULES: THE PROBLEM IN AN ENDEMIC GOITER AREA. J. Martin Miller. New England J. Med. 252:247, 1955.

The published statistics concerning the relationship between thyroid carcinoma and nodular goiter are quite variable and have resulted in conflicting interpretations. Since the internal medicine practice of the Henry Ford Hospital is largely unselected, it presents a reliable opportunity to study this problem in an endemic goiter area. Of six hundred successive female patients over 20 years of age, 4.5% were found to have thyroid nodules of 2 centimeters or more. On the basis of this finding it can be estimated that during the period from 1943 to 1952 nine thousand patients with nodular goiter were registered in the Henry Ford Hospital and Clinic. During this period 435 thyroidectomies were performed for non-toxic nodular goiter. Among these 16 cases of thyroid cancer were found unexpectedly at surgery. The incidence was about the same in cases of solitary nodule as in cases with multinodular goiter. Using these figures for the estimated number of patients with nodular goiter and the number of unsuspected carcinomas found, an incidence of 0.2% unsuspected cancer in nodular goiter can be calculated.

During the 10 year period, 32 new cases of thyroid cancer were seen. In 17 the diagnosis was an unsuspected finding at surgery, and of these only one patient had evidence of recurrent carcinoma in 1953. Of 8 patients presenting with lymphnode metastasis, 7 were living without evidence of any metastasis at the end of the period. A pre-operative diagnosis of carcinoma of the thyroid gland was made in 7 cases, all of whom succumbed to the illness. These data indicate that cancer of the thyroid

is only one-half to one-third as malignment as more common types of cancer. It is felt that cancer found unexpectedly is by nature a slowly growing neoplasm. The removal of all thyroid nodules from patients in the Great Lakes region seems to be a medically impractical and economically unsound approach to the problem of thyroid cancer in nodular goiter.

MECHANISM OF HEMORRHAGE IN IDIOPATHIC THROMBOCYTOPENIC PURPURA. RAYMOND W. MONTO. Fed. Proc. 14:413, 1955.

Cortisone-treated patients with idiopathic thrombocytopenic purpura were studied in respect to clinical course, thrombocyte count, bleeding time, capillary resistance, and in selected patients, capillary microscopy of the nail bed and of sclera, as well as serial skin biopsies at the site at which bleeding times were determined. A marked decrease in hemorrhagic tendency was noted prior to thrombocyte response. This effect is believed to result from the strengthening of the terminal vascular bed by cortisone. The early beneficial results from splenectomy in this disease are also vascular in origin. The site of petechial formation in the nail bed was demonstrated at vascular junctions to the exclusion of the true capillaries. Cortisone produced vasoconstriction of the terminal arterioles, significantly enhancing hemostasis following trauma. It is suggested that mechanism of action of cortisone therapy in the hemorrhagic disorders is: (1) vasoconstriction of muscled blood vessels in the terminal circulation, and (2) collagen sparing in the inhibition of hyaluronidase.

URINARY VITAMIN B^{12} ACTIVITY FOLLOWING INTRANASAL ADMINISTRATION. RAYMOND W. MONTO, AND JAMES T. HOWELL. J. Lab. & Clin. Med. 45:474, 1955.

Two normal subjects were given nasal instillation of 200, 100 and 50 mcg. of crystalline vitamin B^{12}. Two patients with pernicious anemia in relapse received under direct observation 200 and 150 mcg. B^{12} crystals upon the nasal mucosa. Urine collecions were made before and at two hourly intervals after administration of the vitamin and assayed for B^{12} activity. In the normal subjects significant amounts of urinary B^{12} activity were found in the eight hour test period; the greatest excretion occurred in the first two hour period and in proportion to amount of drug administered. The pernicious anemia patients responded in a similar manner; one excreted 12 percent of vitamin given. Following the single application of the vitamin B^{12} crystals to the nasal mucous membranes of the pernicious anemia patients, maximum reticulocyte response of over 40 percent was obtained with eventual complete clinical and hematologic recovery. When vitamin B^{12} is administered orally in the amounts employed in this study, significant amounts cannot be recovered in the urine of either normal subjects or patients with pernicious anemia. The B^{12} excretion patterns obtained in this study are similar to those obtained after parenteral injection of the vitamin. This data would suggest that the vitamin B^{12} is absorbed directly by the nasal mucosa and that intrinsic factor is not required for this utilization.

MEDICAL AND SURGICAL MANAGEMENT OF DIVERTICULITIS IN GERIATRIC PATIENTS. ROBERT J. PRIEST, BROCK E. BRUSH, AND LOUIS J. GREGORY. J. Amer. Ger. Soc. 3:55, 1955.

Diverticula of the colon are frequently found in the course of barium enema x-ray studies. Only a small percentage of such patients with diverticulosis coli developed a complication of diverticulitis. The incidence of diverticulitis has increased with the changing age pattern of the population. Conservative medical management is recom-

mended for uncomplicated diverticulitis in geriatric patients. Surgical intervention is usually indicated in such complications of diverticulitis as perforation, abscess formation, obstruction, fistula formation and hemorrhage. The complication of obstruction occurred in 26% of the geriatric patients studied. When hemorrhage occurs a differential diagnosis from carcinoma of the colon must be made. The procedure recommended for most geriatric patients with surgical complications of diverticulitis is a three- stage resection of the involved segment of colon.

COMBINED ANTIBIOTIC AND CORTISONE THERAPY IN CLINICALLY SEVERE INFECTIOUS MONONUCLEOSIS. E. L. Qinn, D. C. Bunch and Muriel Carson. In Welch, H. and Marti-Ibanex, F., Eds. Antiboitics Annual, 1954-55. New York, Medical Encyclopedic, Inc., 1955, p. 56.

Five clinically severe cases of infectious mononucleosis were treated by the simultaneous administration of cortisone and antibiotics. Dramatic subjective and objective improvements were noted by (1) rapid lysis of sore throat, pharyngeal inflammation and edema, (2) decrease in fever, and (3) decreased general toxicity. A moderately rapid regression of lymphadenopathy, splenomegaly and hepatometgaly frequently occurred. The percentage of atypical lymphocytes in the peripheral blood in one case dropped sharply. Heterophile agglutination was unaffected. Clinical relapse occurred with early withdrawal of cortisone. It is believed that such therapy is a worthwhile measure for judicious use in cases of infectious mononucleosis of greater than average severity.

STUDY OF THE L. E. PHENOMENON IN INVESTIGATIVE LESIONS IN PATIENTS WITH ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS. J. W. Rebuck. Fed. Proc. 14:417, 1955.

The ability of the individual patient with acute disseminated lupus erythematosus to produce the cellular lesions was assessed within the patient himself. In the first patient who was in a state of therapeutic adrenal hypercorticism the lesion failed to present L. E. cells although her marrow test was positive. In the subsequent 4 patients with the disease, 3 exhibited L. E. cells in non-specific experimental lesions, while 2 lesions in the remaining patient contained L. E. cells only after the local application of her own L. E. factor containing serum.

PART II. TECHNIQUES IN THE STUDY OF LEUKOCYTIC FUNCTIONS. A METHOD OF STUDING LEUKOCYTIC FUNCTIONS *IN VIVO*. John W. Rebuck and James H. Crowley. Ann. New York Acad. Sci. 59:757, 1955.

This paper constitutes the presentation of the control work for the human skin windows, by which the cellular exudates of single lesions in man were sampled hour by hour. When the exciting antigen was one to which the human subject was not systemically immunized, transformation of lymphocytes into macrophages was accompanied in the first day by functional and structural changes depicted in 27 illustrations. The participation of blood monocytes in local inflammation was in proportion to the number of monocytes available for emigration or mobilization at the time of inflammation.

AN EXPERIMENTAL AND CLINICAL STUDY OF DEAFNESS FROM LESIONS OF THE COCHLEAR NERVE. Harold F. Schuknecht and Richard C. Woellner. J. Laryngol. & Otol. 69:75, 1955.

This paper consists of a report of an experiment in which the effect on hearing of partial section of the cochlear nerve in cats was related to the audiometric findings

in patients with acoustic neurinoma. Eight cats were behaviourally conditioned so that hearing tests could be done on them. In a sterile operation a partial section of the cochlear nerve then was performed on each animal. A detailed study was then made of the histological and functional changes resulting from these lesions. The following information was acquired.

1. Both high and low frequency hearing losses were produced separately by selective section of fibres of the cochlear nerve, thus demonstrating that frequency has a spatial representation within the cochlear nerve trunk.
2. Quantitative histological studies of several cochleae revealed that up to 75 per cent of nerve fibres to particular regions were destroyed without creating threshold elevations for frequencies having their fields of excitation in those regions, whereas greater nerve fibre losses did create threshold elevations.
3. Six cochleae with varying degrees of cochlear nerve degeneration had normal organs of Corti which confirmed the concept that the nerve fibres are anatomically and metabolically independent of the hair cells.
4. Four ears had degenerative changes in the membranous labyrinths which were presumed to have resulted from injury to the nutrient vessels of the labyrinth. The findings suggested that three types of injury to the nutrient arterial supply were created: (a) partial injury to cochlear artery, resulting in damage to the apical half of the cochlea; (b) severe injury to the cochlear artery, resulting in damage to all of the cochlea except the extreme basal end; (c) severe injury to both cochlear and vestibular arterial supply resulting in damage to both cochlear and vestibular membranous labyrinths.
5. Histological evidence derived from one cochlea suggests, but does not yet prove, that the fibres of the olivo-cochlear bundle terminate on the inner hair cells.

Two human patients with proven acoustic neurinomas were found to have abnormally poor speech discrimination in relation to the pure tone thresholds in the involved ears. In one case there were normal pure tone thresholds for the three speech frequencies and a discrimination score of 16 per cent, and in the other case there was an average loss for speech frequencies of 42db and a speech discrimination score of zero. Patients having pure tone threshold losses of similar magnitude from lesions of the organ of Corti exhibit a less severe loss of speech discrimination.

Thus, from the results of the animal experiments and findings in the human ears it is evident that only a small number of cochlear nerve fibres are necessary to conduct an impulse of threshold magnitude, but that greater numbers of nerve fibres are needed to conduct the complex neural patterns of speech.

ENZYMATIC PATHWAYS IN THE DEGRADATION OF SULFUR-CONTAINING AMINO ACIDS. Thomas P. Singer and Edna B. Kearney. In McElroy, W. D., and Glass, B., Ed. Baltimore, The Johns Hopkins Press, 1955, p. 558.

PROSTHETIC GROUP OF SUCCINIC DEHYDROGENASE. Thomas P. Singer and Edna B. Kearney. Fed. Proc. 14:282, 1955.

The authors have previously reported the solubilization and purification of succinic dehydrogenase (Biochim. et biophys. acta, 15:151). This is the primary dehydrogenase in the chain of proteins linking the oxidation of succinate to the reduction of cytochrome c, and is characterized by its inability to react with dyes other than phenazine derivatives. The highly purified enzyme (close to homogeneous in the ultracentrifuge) contains no hemin and no significant amount of any of the known water-soluble vitamins except

alpha-lipoic acid (170 gamma/gm.). It is not yet known whether the latter is an impurity or a functional component. Among metal ions only iron is present in significant concentration (1M/135,000 g. in the best preparations). The iron is entirely liberated by trichloroacetic acid with consequent disappearance of the amber color of the dehydrogenase. The color is also bleached partially by hydrosulfite and by succinate; malonate inhibits the bleaching by succinate. This and other data suggest that iron is a prosthetic group of succinic dehydrogenase and that the amber color is due to the iron-protein bond, as in the beta-globulin of plasma. The iron is extremely tightly bound by the enzyme. o-Phenanthroline does not dissociate the iron but forms a red chelate with the holo-enzyme which remains fully active. In addition to ferrous iron, inorganic phosphate plays a role in the activity, since the latter is dependent on added phosphate, which is not replaceable by arsenate.

THE HYPOPHYSEAL GROWTH HORMONE, NATURE AND ACTIONS. ed. by RICHMOND W. SMITH, JR., OLIVER H. GAEBLER AND C. N. H. LONG, New York, McGraw-Hill Book Co., Inc., 1955.

In this volume are recorded the complete proceedings of an international symposium, The Hypophyseal Growth Hormone, Nature and Actions, which was held at the Henry Ford Hospital on October 27, 28, and 29, 1954 and sponsored jointly by the Hospital and the Edsel B. Ford Institute for Medical Research.

X-RAY AND ELECTRON MICROSCOPE ON ALUMINUM OXIDE TRIHYDRATES. JOHN H. L. WATSON, JONATHAN PARSONS, A. VALLEJO-FREIRE, AND P. SOUZA SANTOS. Kolloid Zeit. 140:102, 1955.

Gels and sols of aluminum oxide trihydrate were prepared by five different methods and studied by x-ray diffraction and electron microscopy. The x-ray diffraction analysis has shown that all methods produce mixtures of Gibbsite and Bayerite, the relative proportions of each varying from method to method. A sol and gel prepared by the same method present identical x-ray difffraction patterns and their morphologies are similar in the electron microscope. Two main particle shapes were observed: hexagonal prisms and triangular somatoids. There is experimental evidence which indicates that the former are Gibbsite and the latter, Bayerite. On this basis Willstaetter's methods seem to produce more Bayerite than Gibbsite. The reverse was true for Kraut's method, while in Fricke and Jockers' method, almost pure Bayerite was produced. A platelet structure is proposed for the triangular somatoids.